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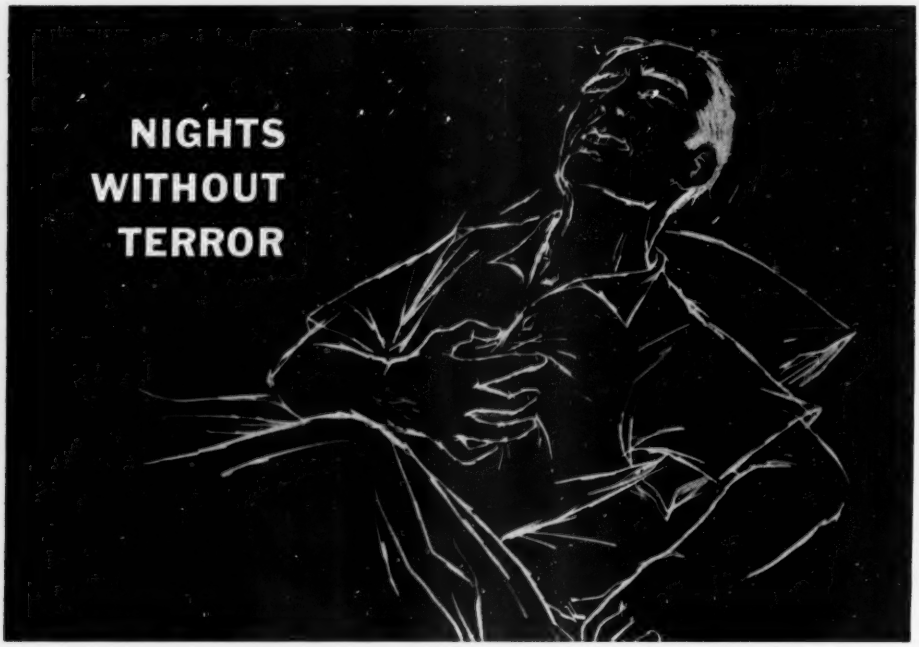

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1. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: New York State J. Med. 52:2012 (Aug. 15) 1952.
3. Perlman, A.: Angiology 3:16 (Feb.) 1952.

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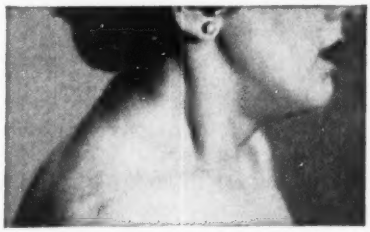
[1]Evans, R. R., and Rackemann, F. M.: *A.M.A. Arch. Int. Med.* **90**:96–127, July 1952.



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3. Armbrust, Chas. A. Jr. and Levine, Samuel A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases: Circulation, 1; 28-39 (Jan.) 1950
4. Bell, G. O.; Bradley, R. B.; and Hurxthal, L. M.: Paroxysmal Tachycardia, Experiences with Massive Doses of Quinidine Intravenously in a Refractory Case: Circulation, 1: 939 (April Part II) 1950

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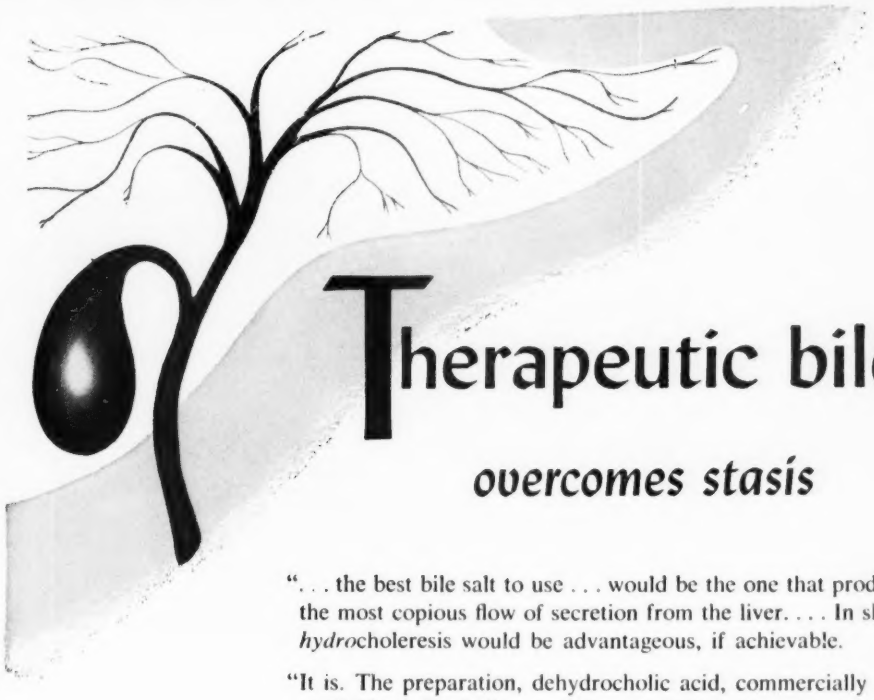

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*Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 361.

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CORTICOTROPIN (ACTH) AND ADRENAL HORMONES DURING OPERATIVE STRESS IN ENDOCRINE DISEASE

LAURENCE H. KYLE, M.D.
WILLIAM P. WALSH, M.D.
AND
LIEUTENANT PAUL D. DOOLAN (MC), U.S.N.
WASHINGTON, D. C.

WIDESPREAD interest in the application of corticotropic and steroid hormone therapy to a diverse number of unrelated nonhormonal diseases has overshadowed the value of these drugs in endocrine disorders. This article deals with the more logical and specific application of the newer hormone preparations to endocrine deficiency states, with special emphasis on their value for protection against operative trauma. Poor response to surgical stress is a dominant feature of many deficiency states but is particularly significant in panhypopituitarism, Addison's disease, and functioning adrenal tumors with contralateral adrenal atrophy.

PITUITARY DEFICIENCY

Surgical therapy is a frequent necessity in the treatment of patients with pituitary failure, not only because the basic disease process often requires operative intervention, but also for the reason that these patients are subject to many of the surgical conditions which affect the endocrinologically normal population. Under conditions of stress, either incidental or coincidental to the basic glandular disease, patients with panhypopituitarism must include with their surgical risk the probability of a high mortality and prolonged morbidity.[1] The major difficulties, most prominent in previously untreated patients, are related to three factors: (1) the debilitated condition of the patient, especially with respect to his depleted protein stores; (2) the difficulty of the individual in maintaining normal carbohydrate metabolism, and (3) impairment of production of hormones instrumental in protecting the patient against severe stress. For adequate protection of the hypopituitary patient at operation there are therefore two therapeutic necessities: institution of measures to promote adequate protein storage prior to surgery and assurance of an adequate supply of adrenal hormone during the operative and early postoperative period. The first requirement may be fulfilled by administration of an anabolic com-

Dr. Walsh is William Wade Hinshaw Cancer Research Fellow.

From the Department of Medicine, Georgetown University Hospital and Georgetown University School of Medicine.

This study was supported by the William Wade Hinshaw Cancer Research Fund. Presented in part at the Southern Section, American Federation for Clinical Research, New Orleans, 1951.

1. Grant, F. C.: Surgical Experience with Tumors of the Pituitary Gland, J. A. M. A. **136**:668-672, 1948.

pound—usually testosterone—together with a diet containing adequate calories and protein. The need for adrenal hormone may be met by giving corticotropin (ACTH) for several days preoperatively; it is necessary to provide a longer period of stimulation in the hypopituitary patient than in the person with an intact pituitary-adrenal system, because of the adrenal atrophy which results from prolonged corticotropin deficiency.[2] As an alternative, cortisone or adrenal extract may be used during and after operation, this method of therapy being especially necessary if time does not permit proper preparation with corticotropin or if the atrophic adrenals fail to respond to stimulation by that hormone.

The following three cases illustrate the management of patients with hypopituitarism who require surgical therapy.

CASE 1.—A 19-year-old youth was admitted to the neurosurgical service in June, 1949, because of a steady decrease in visual acuity. The history and physical examination revealed features typical of panhypopituitarism, as well as an episode of marked polyuria at the onset of his illness one and one-half years previously. There was a right homonymous hemianopsia, and, although the sella turcia appeared normal on x-ray examination, a diagnosis of pituitary

Laboratory Findings in Case 1

Insulin Tolerance Test (0.05 μ/Kg.)		Mayo Water Test	
Fasting	87 mg./100 ml.	Night spec.	455 cc.
20 minute	39 mg./100 ml.	1st day spec.	120 cc.
30 minute	33 mg./100 ml.	2d day spec.	100 cc.
45 minute	43 mg./100 ml.	3d day spec.	130 cc.
60 minute	45 mg./100 ml.	4th day spec.	160 cc.
90 minute	50 mg./100 ml.		

Eosinophile Response			
Epinephrine (0.5 Mg.)	Control	4 Hr.	
Corticotropin (40 mg. Intramuscularly)	598 944	589 899	
Protein-bound Iodine	4.3, 4.4 mμ	Serum Na	142 mEq./L.
24 hour I^{131} uptake	8.9%	Serum K	4.5 mEq./L.
B. M. R.	−44%-41%	Serum Cl	109 mEq./L.
Cholesterol	264 mg./100 cc.	Serum CO_2	28 mEq./L.

Urinary 17-ketosteroids	1.3, 2.0, and 0.6 mg.
Pituitary gonadotropins ("F. S. H.")	negative for 6 m. u.

tumor was made. Because of the patient's debilitated condition, he was transferred to a medical ward in order to obtain complete hormonal evaluation and adequate preoperative preparation.

Laboratory studies (Table) demonstrated the usual findings of complete pituitary failure. The patient was given supplemental sodium chloride and daily injections of testosterone propionate, but only moderate improvement resulted until the caloric and protein intakes were increased. A steady increase in strength and alertness and an 8-lb. (3.6-kg.) gain in weight occurred during the following two weeks. The hematocrit reading rose from 34 to 42%, and the serum proteins increased from 5.9 to 6.7 gm. per 100 ml. of blood.

Because of progressive visual impairment during this time, a craniotomy was performed, protective hormonal therapy with adrenal cortex extract being provided. A soft tumor mass lying beneath the optic chiasm and involving the left optic nerve was removed as completely as possible. Microscopical examination of the tissue showed malignant cells suggestive of a chromophobe pituitary tumor.

2. Knowlton, A. I.; Jailer, J. W.; Hamilton, H., and West, R.: Effects of Pituitary Adrenocorticotrophic Hormone (ACTH) in Panhypopituitarism of Long-Standing and in Myxedema, Am. J. Med. **8**:269-284, 1950.

As shown in Chart 1, large amounts of aqueous adrenal cortex extract and lipo-adrenal cortex were given during and immediately after operation, together with frequent infusions of glucose and water. The postoperative course was free of complications for three days, but on the fourth day there occurred hypotension, bradycardia, and progressive clouding of the sensorium. These symptoms continued, and on the fifth postoperative day the patient began to vomit. The serum potassium was 5.9 mEq. per liter and the blood sugar 69 mg. per 100 ml. of blood. The administration of 1,000 cc. of glucose and saline and 5 cc. of lipo-adrenal cortex resulted in definite improvement. Within four hours the patient was able to retain fluids administered orally, and during the following 12 hours he ingested 12 gm. of sodium chloride. The blood pressure rose to preoperative levels, the pulse rate became normal, and during the sixth postoperative day the patient was able to retain fluid, solid food, and supplemental sodium chloride. Convalescence was uncomplicated from that point onward. As shown in Chart 1, a marked eosinopenia followed surgery and persisted for 48 hours.

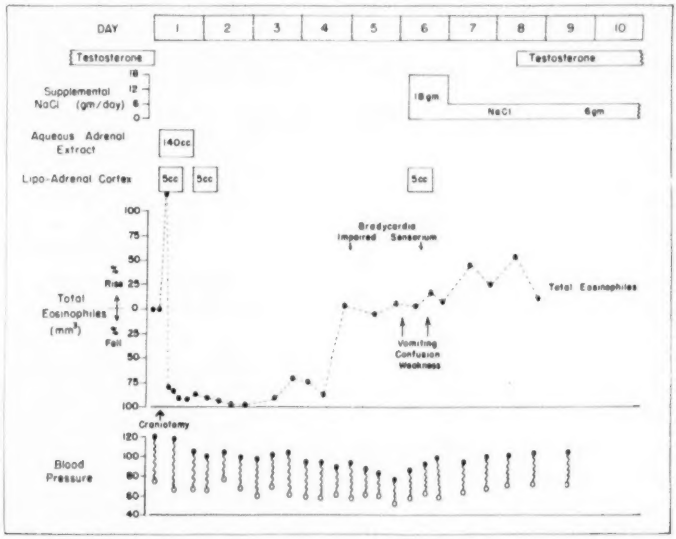

Chart 1.—Course in Case 1.

Summary.—This young man showed the cardinal features of total pituitary failure and was in extremely poor general condition. The administration of testosterone together with an adequate protein and caloric intake brought about marked general improvement. The use of large amounts of adrenal cortex extract at the time of operation and in the early postoperative period allowed the usual response to traumatic stress and satisfactorily maintained his general condition. Clinical deterioration, apparently due to excessive salt loss, was corrected by the administration of sodium chloride. Eosinopenia was more marked and persisted for a longer period than could be readily accounted for by the steroid hormone therapy.

Case 2.—A 53-year-old man was admitted to the hospital in September, 1950, suffering from severe obstructive jaundice. One year previously a diagnosis of hypopituitarism had been made after the patient went into shock during an attempt at making an arteriogram to ascertain the site of a spontaneous subarachnoid hemorrhage. At that time there was clinical evidence of hypogonadism and hypothyroidism, the latter having responded very poorly to desiccated thyroid hormone. Laboratory studies confirmed the existence of hypofunction of gonads and thyroid secondary to pituitary insufficiency. At a later date, injection of 40 mg. of corticotropin produced no adrenal response, eosinophiles decreasing only from 340 to 330 per cubic millimeter. Results of an insulin tolerance test were characteristic of hypoglycemic unresponsiveness, and

only minimal eosinopenia followed this stimulus. The urinary 17-ketosteroid excretion was 1.9 and 1.2 mg. in 24 hours. Until the occurrence of jaundice the patient had been maintained in excellent health by the administration of thyroid and testosterone.

Evidence of biliary obstruction had appeared five weeks prior to admission, and during the interval there had been steady loss of weight amounting to 17 lb. (7.7 kg.). Even though it appeared probable that the jaundice was associated with methyltestosterone therapy (as reported in a separate communication [3]), x-ray evidence of a duodenal lesion and the opinion of the surgical consultant that the gall bladder was palpable indicated the necessity of surgical intervention. Consequently the patient was given daily intravenous injections of corticotropin, the response to which is shown in Chart 2. After seven days of corticotropin therapy an abdominal exploration was done. This revealed no evidence of biliary obstruction, but a liver biopsy showed a histological pattern consistent with that occurring in jaundice associated with methyltestosterone therapy. Although there occurred moderate hypotension immediately after operation, this responded readily to ephedrine. The remainder of the postoperative course was uneventful except for the occurrence of a severe psychotic reaction which lasted 10 days.

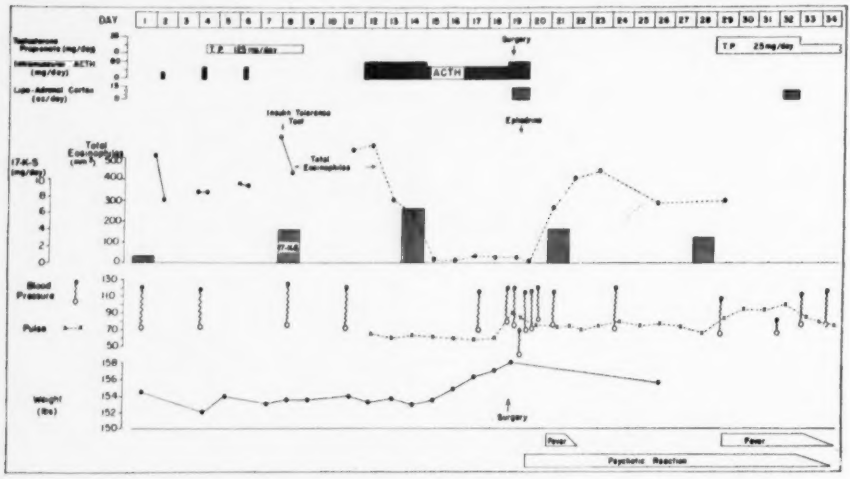

Chart 2.—Course in Case 2.

Summary.—This middle-aged white man had severe panhypopituitarism manifested clinically by evidence of thyroid and gonadal failure. Laboratory study showed secondary insufficiency of all target glands. His general condition was fairly good, but anorexia prevented adequate preoperative preparation. The use of corticotropin for several days prior to surgery and of adrenal cortex extract during operation appeared to prevent the postoperative complications frequently seen in this type of patient. The postoperative psychosis may have been secondary to corticotropin therapy, inasmuch as patients with pituitary insufficiency may be especially prone to psychic disturbances following stimulative treatment.[4]

CASE 3.—A 20-year-old woman was admitted to the neurosurgical service in August, 1951, with the complaint of progressive failure of vision. Seven months previously, after three weeks of severe headache, vision in the right eye began to fail, and at the time of admission the patient could distinguish only light and dark with that eye. The left visual field appeared normal, and an x-ray of the skull showed marked enlargement of the sella turcica. The patient had no

3. Brick, I. B., and Kyle, L. H.: Jaundice of Hepatic Origin During the Course of Methyl-Testosterone Therapy, New England J. Med. **246**:176-179, 1952.

4. Summers, V. K., and Sheehan, H. L.: Cortisone and ACTH in Hypopituitarism, Brit. M. J. **2**:564-568, 1951.

symptoms or signs suggestive of either hypoadrenalism or hypothyroidism. The breasts and external genitalia were normally developed, and sexual hair was abundant. The patient had never experienced menstruation despite numerous attempts to induce a cycle by administration of hormones.

Although it appeared improbable that the amenorrhea was secondary to pituitary failure, its existence suggested the desirability of studying the functional response of the adrenal gland, and therefore an intravenous corticotropin test was performed. After an eight-hour infusion of 25 mg. of corticotropin, the total eosinophiles decreased only from 300 to 160 per cubic millimeter. Collection of urine for determination of 17-ketosteroids was started and daily infusions of corticotropin continued. After the second day of corticotropin therapy the total eosinophile count was 310 per cubic millimeter and the patient excreted only 2.9 mg. of 17-ketosteroids in 24 hours. After 5 days of intravenous corticotropin therapy the 17-ketosteroid excretion was 6.1 mg. in 24 hours and the total eosinophile count had fallen to 8 per cubic millimeter.

Craniotomy was then performed, and a chromophobe pituitary tumor was removed. The patient's postoperative course was relatively uncomplicated, considering the radical nature of the surgical procedure, there occurring only a moderate hyperthermia for five days. Twenty-four hours after operation the total eosinophile count was 24 per cubic millimeter, and after complete recovery from the operation the patient excreted less than 2 mg. of urinary 17-ketosteroids a day.

Summary.—This young woman showed the mechanical disturbances associated with expanding pituitary lesions. The presence of amenorrhea suggested the possibility of hypopituitarism, and because of an inadequate eosinopenic response to an intravenous corticotropin test, this drug was given for several days preoperatively. The patient tolerated operation well, and it was apparent after specimens of urine were analyzed for 17-ketosteroids that marked adrenal insufficiency had been present.

The study of these three patients helps to define a number of problems. The first problem is to decide which patients should be given special care prior to pituitary surgery. Since the gonadotropins are usually the first tropic hormones to be affected in pituitary failure, lack of evidence of gonadal failure, manifested by either amenorrhea or impotence, would seemingly indicate the existence of adequate secretion of pituitary hormones. On the other hand, patients may have nearly total gonadal failure and yet, by maintenance of corticotropin production, possess the ability to respond to trauma by increasing the secretion of adrenal hormones. We believe that any patient with a pituitary lesion should be carefully studied for evidence of target gland failure, and if any deficiency is disclosed, adequate treatment, especially with corticotropin, should be administered prior to operation. Because of the difficulty in quantitating adrenal reserve, it is probably best to treat any patient with a pituitary lesion and evidence of gonadotropin deficiency as if he had failure of production of all tropic hormones. Opinion has been offered in the literature to the effect that patients with any type of suprasellar lesion should be given cortisone at the time of surgery irrespective of the apparent state of the target glands.[5] In any event, it should be emphasized that the possibility of pituitary failure and need for treatment should be given careful consideration prior to conduct of any operative procedure in or near the pituitary gland.

The second problem posed by these patients shifts the emphasis from the adrenal hormones to the other target gland hormones which may be deficient in hypopituitarism. With the exception of anabolic steroids, produced by the adrenals of both sexes and the testes of the male, these hormones appear to be less important as an adjunct to surgical therapy. Certainly the germ-cell stimulating aspects of the

5. Ingraham, F. D.; Matson, D. D., and McLaurin, R. L.: Cortisone and ACTH as an Adjunct to the Surgery of Craniopharyngiomas, New England J. Med. **246**:568-571, 1952.

gonadotropins are of minor importance during periods of stress, and lack of thyroid hormone is significant only so far as it may lessen the effect of cortical hormones on body tissues or decrease adrenocortical responsiveness.[6] Thus only the adrenal hormones, both anabolic and antianabolic, are of vital importance.

Third, the physician must consider which of the numerous metabolic changes following operative trauma are the important indications of normalcy of the organism and thus to be considered desirable in promoting survival. This controversial problem is difficult to evaluate.

Marked increase in urinary nitrogen excretion has been noted almost uniformly after the trauma of major surgical procedures.[7] Neither the mechanism of this apparent catabolic reaction nor its exact meaning in terms of benefit have, as yet, been clearly delineated. Views as to its place in homeostasis vary from the older idea that nitrogen loss is extremely detrimental to body economy, through the concept that protein breakdown is solely for the purpose of obtaining glucose, to the opinion that the body attempts to bring smaller protein moieties or even carbon fragments to the site of injury for assistance in speeding reparative processes. None of these concepts have been proved. With respect to the mechanism of negative nitrogen balance, the observation that increased nitrogen excretion follows either adrenal stimulation or administration of adrenal hormones suggested that the protein catabolic response to surgery was secondary to action of adrenal corticoids. However, the observation of Ingle and his associates that a negative nitrogen balance accompanies trauma in adrenalectomized rats maintained on small doses of adrenal cortex extract indicates that, although some adrenal hormone is necessary in order that the catabolic response may occur, the mechanism is not dependent upon increased adrenal activity.[8] The lack of significant post-traumatic protein breakdown in debilitated patients [9] and protein-depleted animals [10] strongly suggests that the magnitude of negative nitrogen balance is at least partially dependent upon the adequacy of protein reserves.

Clinically it has been observed that patients who fail to show adequate nitrogen excretion after surgical procedures respond poorly,[11] and a similar correlation

6. Wolfson, W. Q.; Beierwaltes, W. H.; Robinson, W. D.; Duft, I. F.; Jones, J. R.; Knorpp, C. T.; Siemiensky, J. S., and Eya, M.: Corticogenic Hypothyroidism: Its Incidence, Clinical Significance and Management During Prolonged Treatment with ACTH, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, New York, The Blakiston Company, 1951, Vol. 2, pp. 95-115.

7. Howard, J. E.: Protein Metabolism During Convalescence After Trauma: Recent Studies, Arch. Surg. **50**:166-170, 1945. Peters, J. P.: Effect of Injury and Disease on Nitrogen Metabolism, Am. J. Med. **5**:100-109, 1948.

8. Ingle, D. J.; Ward, E. O., and Kuizenga, M. H.: The Relationship of the Adrenal Glands to Changes in Urinary Non-Protein Nitrogen Following Multiple Fractures in the Force-Fed Rat, Am. J. Physiol. **149**:510-515, 1947.

9. Moore, F. D., and Ball, M. R.: The Metabolic Response to Surgery, Springfield, Ill., Charles C Thomas, Publisher, 1952. Browne, J. S. L., in Conference on Metabolic Aspects of Convalescence, Sixth Meeting, edited by E. C. Reifenstein Jr., Josiah Macy Jr. Foundation, 1944, p. 67.

10. Cuthbertson, D. P.: Protein Intake and Metabolism in Relation to Wound Healing, in Josiah Macy Jr. Foundation Conference on Metabolic Aspects of Convalescence, Fifth Meeting, edited by E. C. Reifenstein Jr., 1943, p. 44 (Author's Summary).

11. Browne, J. S. L., in Josiah Macy Jr. Foundation Conference on Metabolic Aspects of Convalescence, Ninth Meeting, edited by E. C. Reifenstein Jr., 1945, p. 15.

between lack of catabolic response and clinical deterioration has been seen following pituitary surgery.[12] Thus it appears logical to conclude that the normal organism should show increased protein excretion after traumatic stress and that this can be provided even in the malnourished hypopituitary person. Although there does not appear to be need for a great excess of 11-17-oxysteroids, the presence of some of these materials seems essential, and, perhaps more important, the patient must have abundant protein stores. Activation of the atrophic adrenals with administration of corticotropin or use of adrenal hormone meets the first requirement; administration of testosterone and food satisfies the second.

Another constant occurrence in the normal person is the eosinopenia which follows surgery.[13] Although the value of this phenomenon is unknown, its mechanism appears to be largely dependent upon an intact pituitary-adrenal axis. Despite the lack of clear understanding regarding the importance of the eosinopenic reaction, its occurrence can be construed as an indication of normalcy, and efforts should be made, even if artificial, to effect its production. In addition, the change in eosinophiles is of both diagnostic and therapeutic value, indicating a qualitative defect in the patient's adrenal response and serving as a rough guide to the adequacy of substitution therapy.

Patients with hypopituitarism show less abnormality of electrolyte control than of other metabolic functions mediated through action of the adrenal hormones,[14] but during periods of stress excessive sodium loss can occur. Consequently, although cortisone and adrenal cortex extract probably contain sufficient "salt-retaining" principle to make administration of desoxycorticosterone unnecessary, sodium should be administered much earlier in the postoperative period and in larger amounts than is considered necessary or desirable in the usual surgical case. Failure to fully appreciate this fact appears to have complicated the problems and delayed the recovery of our first patient.

Thus, available evidence indicates that the hypopituitary patient should be prepared for surgery with a high-protein diet and the use of an anabolic steroid, that an adequate catabolic and eosinopenic reaction should be provided by use of either corticotropin or adrenal 11-17-oxysteroids, and that sodium should be given earlier and in larger amounts postoperatively than in the usual surgical case. One last problem remains; that is, whether the patient whose atrophic adrenals have been stimulated preoperatively by corticotropin will experience adequate adrenal stimulation after surgery in the absence of endogenous corticotropin production. Definite information regarding the complete dependence of increased adrenal activity on corticotropin is lacking, although the persistence of eosinopenia in Case 1 suggests either direct stimulation of the adrenal or eosinopenia secondary to factors other than production of 11-oxygenated steroids. Until more information is acquired it would be best either to continue administration of corticotropin well into the postoperative period or to administer adrenal hormone during and immediately after surgery.

12. Howard, J. E., in Josiah Macy Jr. Foundation Conference on Metabolic Aspects of Convalescence, Eighth Meeting, edited by E. C. Reifenstein Jr., 1944, p. 26.

13. Roche, M.; Thorn, G. W., and Hills, A. G., The Levels of Circulating Eosinophils and Their Response to ACTH in Surgery, New England J. Med. **242**:307-314, 1950.

14. McKay, D. G.; Burnett, C. H., and Burrows, B. A.: Panhypopituitarism: Case Report Correlating Clinical and Pathological Findings, J. Clin. Endocrinol. **10**:540-555, 1950.

ADDISON'S DISEASE

The points discussed with respect to the problems of operative stress in hypopituitarism are with certain exceptions applicable to adrenal insufficiency. In Addison's disease the adrenal failure is complete and leads to a more marked disturbance of electrolyte metabolism. The adrenal cannot be stimulated with corticotropin, and thus adrenal corticoids must be used. Although male patients with primary adrenal failure have adequate anabolic hormone, in the female the deficiency of androgen is of the same magnitude as in hypopituitarism. In addition, one complication which results in severe stress—pregnancy—is most unusual in hypopituitarism, for even with partial pituitary insufficiency the gonadotropins are ordinarily affected. The following case illustrates the problems encountered in the management of pregnancy in a patient with Addison's disease.

CASE 4.—A 25-year-woman with Addison's disease of eight years' duration was first seen in June, 1950, when seven and one-half months pregnant. She had been maintained in good health by desoxycorticosterone, diethylstilbestrol (stilbestrol®), and occasional injections of adrenal cortex extract during the initial course of this pregnancy. Fifteen months previously the patient had come to term with her first pregnancy and had undergone an uncomplicated delivery save for premature rupture of the membranes. The infant died shortly after birth, and a severe Addison's disease crisis developed in the patient early in the postpartum period.

During the last trimester of the second pregnancy the patient was well maintained, being in better health and requiring less desoxycorticosterone than usual. The urinary 17-ketosteroids increased to 5 mg. a day during the latter part of pregnancy, returning to the usual level of 1.5 mg. a few days prior to delivery. On the day of expected delivery she was hospitalized, and administration of 3 cc. of lipo-adrenal cortex and 25 mg. of cortisone daily by intramuscular injection was started. After four days of this treatment gentle induction of labor was attempted but as this met with no success the patient was discharged, receiving 2 cc. of lipo-adrenal cortex a day. She was readmitted to the hospital five days later after spontaneous rupture of the membranes, and administration of 4 cc. of lipo-adrenal cortex was instituted and 50 mg. of cortisone acetate a day injected intramuscularly. Two days later labor was induced successfully, the patient being given additional amounts of adrenal cortex extract, cortisone, and desoxycorticosterone during labor, as shown in Chart 3. She was delivered of a normal 6-lb. (2,721-gm.) girl, who neither at that time nor in subsequent months showed any clinical features suggestive of abnormal adrenal function. The mother had an entirely uneventful postpartum course, being discharged on the 10th postpartum day, 2 mg. of desoxycorticosterone and 2 cc. of lipo-adrenal cortex a day being prescribed.

Summary.—This young woman had had one previous pregnancy, which resulted in stillbirth, the patient going into crisis during the postpartum period. During the latter part of the second pregnancy the patient showed amelioration of symptoms of adrenal insufficiency. Supportive treatment with adrenal steroid hormones at the time of delivery was accompanied by the uneventful delivery of a normal baby girl, who showed no evidence of either adrenal hyperfunction or deleterious effects of the hormonal treatment.

Recent reviews of the reported instances of pregnancy in Addison's disease stress the frequency of serious complications. In the cases reviewed by Brent it was noted that spontaneous termination of pregnancy at any time before delivery and artificial interruption after the first trimester were accompanied by 100% mortality.[15] Knowlton and her associates called attention to the probability that serious difficulties might be anticipated at the time of delivery because of blood loss and again in the postpartum period as a result of the diuresis which follows withdrawal of progesterone.[16] They also noted the fact that in 8 of the 12 well-docu-

15. Brent, F.: Addison's Disease and Pregnancy, Am. J. Surg. **79**:645-652, 1950.

16. Knowlton, A. I.; Mudge, G. H., and Jailer, J. W.: Pregnancy in Addison's Disease: Report of 4 Patients, J. Clin. Endocrinol. **9**:514-528, 1949.

mented cases, death of the mother occurred during pregnancy or in the early postpartum period.

The first requisite in protecting the mother and baby during delivery is to establish control of the adrenal insufficiency prior to labor. It has been repeatedly observed that patients with Addison's disease are unusually well maintained during the latter part of pregnancy. Observations of Jailer and Knowlton suggest that this improvement is the result of increased adrenal-like hormone, which is supplied by the maternal organism rather than by the fetal adrenal.[17] The existence of increased hormone, probably derived from the placenta, creates not only the problem of complacency, because the patient is doing so well, but also that of rapid withdrawal of endocrine support at a time of severe stress.

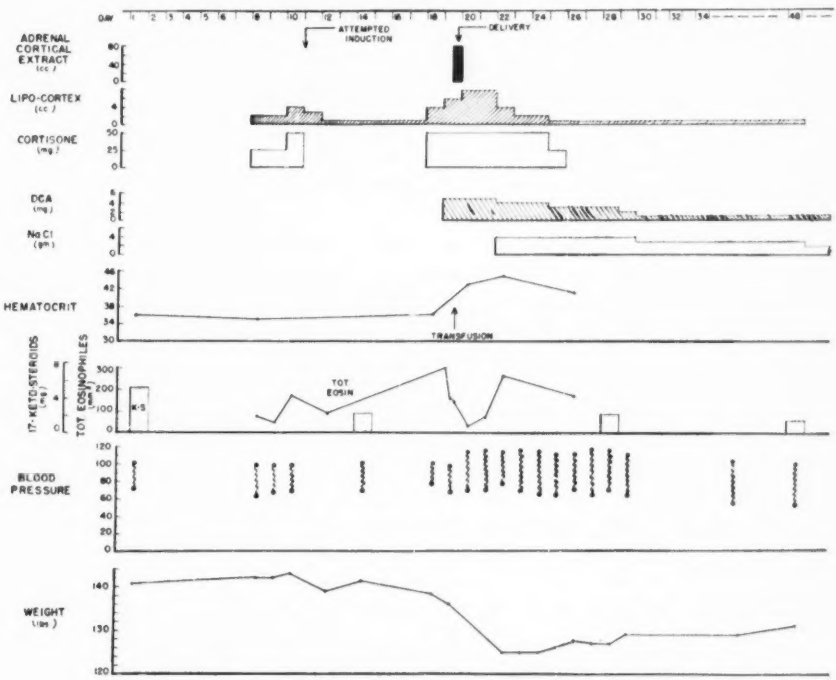

Chart 3.—Course in Case 4.

The management of delivery in Addison's disease, as suggested by Thorn,[18] should be essentially similar to the treatment of a patient with Addison's disease who is undergoing surgery. One important difference must be appreciated. In the instance of an elective operation the date of surgery can be set and treatment commenced a given number of days prior to the traumatic procedure. In pregnancy in Addison's disease the date of expected delivery is far from exact, and the financial

17. Jailer, J. W., and Knowlton, A. I.: Simulated Adreno-Cortical Activity During Pregnancy in an Addisonian Patient, J. Clin. Invest. **29**:1430-1436, 1950.

18. Thorn, G. W.: The Diagnosis and Treatment of Adrenal Insufficiency, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1951.

aspect of treatment has in the past prohibited long-continued administration of adrenal steroids. Because of the latter fact, gentle induction of labor was attempted in our case. Lowering of the cost of cortisone makes it possible to start administration of small doses of this drug several days prior to expected delivery, with a rapid increase in dosage when active labor begins. Because cortisone injected intramuscularly is slow in action and because this synthetic compound may not contain all the factors necessary for a normal response, it is well to administer substantial amounts of adrenal cortex extract during and immediately after delivery, although the development of a preparation of cortisone for intravenous injection may obviate the need for adrenal cortex extract in the future. In addition, desoxycorticosterone acetate should be administered, and sufficient sodium should be supplied the patient. The replacement of blood is of major importance, and early oral feeding should be encouraged. After delivery the dose of cortisone can be gradually decreased, as should that of desoxycorticosterone. With careful attention to details; provision of adequate supplies of cortisone, adrenal extract, and desoxycorticosterone, and use of minimal doses of barbiturate and hypnotics, to which patients with Addison's disease are unusually susceptible, it appears that patients with Addison's disease complicated by pregnancy can be carried through delivery with safety.

REMOVAL OF FUNCTIONING ADRENAL TUMORS

The removal of functioning adrenal tumors, especially of the type associated with the clinical picture known as Cushing's syndrome, is a complicated problem.[19] Because of excessive amounts of circulating 11-17-oxysteroids cause inhibition of corticotropin production, the contralateral adrenal gland undergoes compensatory atrophy. Thus, when the hyperfunctioning tumor is removed the patient is physiologically comparable to one with Addison's disease, with the added factor of severe surgical stress coinciding with sudden withdrawal of an excessive supply of hormone. In addition, patients with overproduction of adrenal 11-17-oxysteroids are protein-depleted, have marked friability of tissues, and are usually in poor general condition for operation.[20] The following case illustrates the type of problem encountered with a functioning adrenal tumor.

CASE 5.—A 23-year-old white woman was admitted to the hospital on April 15, 1951, with a clinical picture consistent with the diagnosis of Cushing's syndrome. Her initial symptoms, including edema, appearance of red abdominal striae, facial hirsuitism, and mild hypertension, had appeared during pregnancy 18 months previously but had regressed almost completely after delivery. Three or four months later the features of Cushing's syndrome returned, and at the time of hospital admission, six months later, there had been a 25-lb. (11.3-kg.) gain in weight, development of roundness of the face, marked plethora, mild acne, hirsuitism, and moderate hypertension. After a few days of hospitalization these features again underwent spontaneous partial regression, and the patient was discharged. During the next three months there was recurrence of all the signs and symptoms of Cushing's syndrome, together with the development of a very marked "buffalo hump," and the patient was readmitted for adrenal surgery. At this time laboratory studies revealed an increase in percentage of polymorphonuclear cells, a

19. Cahill, G. F., and Melicow, M. M.: Tumors of the Adrenal Cortex, J. Urol. **64**:1-25, 1950. Goldberg, M. B.; Gordan, G. S.; Deamer, W. C., and Hinman, F., Jr.: Mortality in Surgically Treated Adrenocortical Tumors: I. Report of Three Cases of Cushing's Syndrome Due to Adrenocortical Tumors, Postgrad. Med. **11**:313-324, 1952.

20. Albright, F.: Cushing's Syndrome: Its Pathologic Physiology; Its Relationship to the Adrenogenital Syndrome and Its Connection with the Problem of the Reaction of the Body to Injurious Agents ("Alarm Reaction" of Selye), Harvey Lect. **38**:123-186, 1942-1943.

serum sodium content of 149 mEq. per liter, a persistently low eosinophile count, and a 17-ketosteroid excretion ranging between 8 and 12 mg. a day.

On Aug. 2, abdominal exploration revealed a small right adrenal gland and a large tumor mass completely replacing the left adrenal gland. Adrenal cortex extract, lipo-adrenal cortex, and cortisone were given during and after the removal of this tumor, as shown in Chart 4. In order to stimulate the atrophic adrenal, corticotropin was administered for several days as the cortisone dosage was decreased. Although this procedure resulted in a temporary increase in urinary 17-ketosteroids, after cessation of corticotropin therapy the 17-ketosteroid excretion dropped to the low postoperative level of 2 mg. a day.

The patient had an uneventful postoperative course and was discharged in good condition on the 17th postoperative day, the urinary 17-ketosteroids being 3.3 mg. and the total eosinophile count being 130 per cubic millimeter on this date. Within four to five days after discharge weakness, anorexia, and mild nausea developed and the patient was again hospitalized. Epinephrine stimulation over a period of 16 hours resulted in a moderate eosinopenic response but did

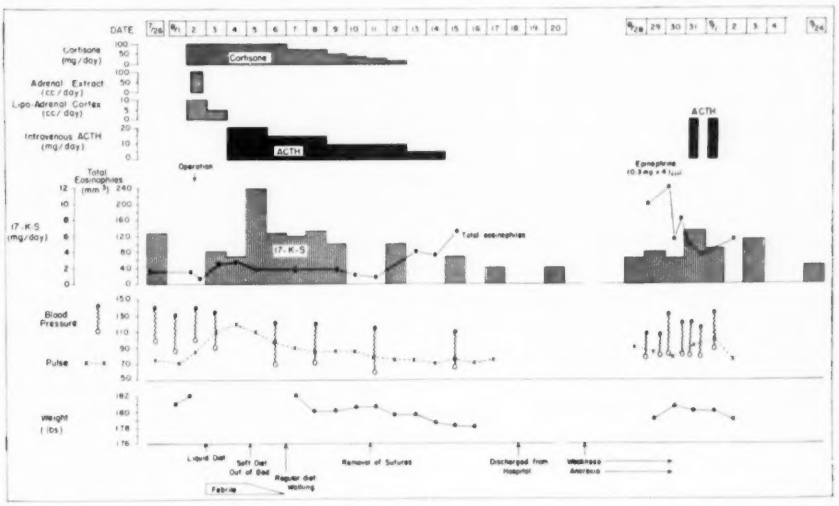

Chart 4.—Course in Case 5.

not cause elevation of the depressed 17-ketosteroids. An eight-hour infusion of corticotropin caused a temporary rise in 17-ketosteroids.

Three to four months after surgery the patient was still weak, listless, and anorectic. She was given cortisone only when these symptoms were unusually severe or during the existence of an upper respiratory infection or similar mild illness. From the third month onward there was gradual but steady improvement in her general condition, and at the present time, approximately one year after operation, the patient shows no evidence of adrenal insufficiency. The urinary 17-ketosteroid excretion continued at very low levels until 10 or 11 months after operation and at the present time averages about 6 mg. a day.

Summary.—This young woman had excessive steroid hormone production of brief duration and thus was in a relatively good condition for operation. She was treated with adrenal cortex extract, cortisone, and lipo-adrenal cortex during and immediately after surgery. She did well on this regimen, although it was apparent that marked adrenal insufficiency was present after removal of the tumor. Despite the fact that some stimulation of the atrophic adrenal could be accomplished with intravenous administration of corticotropin, after cessation of this therapy the patient continued to show signs of poor adrenal function and excreted very small amounts of 17-ketosteroids for several months after surgery.

In patients who have had Cushing's syndrome for any length of time, the protein depletion may be combated with a high protein diet and administration of an anabolic hormone. Although testosterone is ordinarily used, a less potently masculinizing material, such as methylandrostenediol, may be more desirable, especially for females. Potent adrenal cortex hormone should be given at the time of operation, as noted. Although on logical grounds it should be of value to administer corticotropin both preoperatively and postoperatively to stimulate the atrophic adrenal gland, such administration did not appear to be of benefit in the case under discussion. Perhaps there exists a block at the pituitary level, the patient having insufficient endogenous corticotropin production to maintain normal adrenal function even after stimulation of the adrenal has been accomplished. Despite the fact that such patients are obviously deficient in adrenal hormones postoperatively, it must be kept in mind that restoration of normal adrenal function will be delayed if cortisone or adrenal extract is administered continuously in large amounts. It also appears logical that intensive or prolonged use of corticotropin would impede restoration of normal endogenous corticotropin production. Thus it appears best to limit the use of these drugs to periods of stress, sheltering the patient as much as possible from traumatic stimuli during the weeks or months required for normal adrenal function to be regained.

Patients who are to undergo elective adrenalectomy for hypertension and prostatic carcinoma present essentially the same problem and can be managed in much the same fashion.[21] Similarly, the use of cortisone has lowered the mortality and apparently prevented the severe postoperative problems formerly frequent in the case of adrenal resection for Cushing's syndrome due to bilateral adrenal hyperplasia.[22] Patients with the adrenogenital syndrome are not ordinarily such serious operative problems except in some instances of congenital adrenal hyperplasia. The presence of excessive androgenic hormone is beneficial rather than harmful to the patient's general condition, and because androgen is not a potent depressant of corticotropic hormone, contralateral adrenal atrophy is less frequent.

Although the use of adrenal hormones at the time of surgical removal of adrenal pheochromocytomas has been recommended,[23] we do not believe that there exists any need for such treatment except under unusual circumstances. In such instances, as for example after removal of bilateral chromaffin-cell tumors with consequent marked adrenal trauma, adrenal cortex extract could be administered intravenously in large amounts, after which the patient's status could be maintained with cortisone until restoration of adrenal function was attained. If there exists any type of adrenal insufficiency warranting the use of cortisone or adrenal cortex extract, these drugs should be given in large amounts. It is better to withhold hormones, studying the patient's need, or to administer large doses on an empirical basis, than to give totally inadequate amounts under the misconception that possible adrenal insufficiency justifies minimal treatment.

21. Zintel, H. A.; Wolferth, C. C.; Jeffers, W. A.; Hafkenschiel, J. H., and Lukens, F. D. W.: Subtotal Adrenalectomy in the Treatment of Patients with Severe Essential Hypertension, Ann. Surg. **134**:351-360, 1951.

22. Priestley, J. T.; Sprague, R. G.; Walters, W., and Salassa, R. M.: Subtotal Adrenalectomy for Cushing's Syndrome, Ann. Surg. **134**:464-472, 1951.

23. Richards, V., and Hatch, F. N.: Surgical Experiences with Pheochromocytoma, Ann. Surg. **134**:40-54, 1951.

SUMMARY

Marked intolerance to surgical trauma is a common characteristic in hypopituitarism, Addison's disease, and Cushing's syndrome after removal of an adrenal tumor. Although this is in large part due to inadequate production of adrenal oxysteroid hormones, the protein depletion secondary to malnutrition and deficiency of anabolic hormones may be a significant contributing factor. Consequently, in each of these conditions, therapy should provide preoperative protein repletion, as well as adequate amounts of circulating 11-oxysteroids at the time of operation.

Prior to any surgical procedure in the pituitary region, the patient should be carefully studied for evidence of pituitary insufficiency. Demonstration of such insufficiency, especially if there is adrenal insufficiency secondary to corticotropin deficiency, indicates the need for special therapeutic measures. Protein repletion may be accomplished with a diet high in calories and protein, together with administration of an anabolic hormone. Several days of corticotropin therapy prior to operation may provide adequate adrenal activation, but if this fails to occur or if time prohibits trial of such treatment, cortisone and adrenal extract should be given in large amounts.

Any type of traumatic procedure, including labor, may be extremely formidable in the patient with either hypopituitarism or chronic adrenal insufficiency, but intensive hormonal therapy will greatly lessen the risk of such procedures. In the case of any chronically ill patient consideration should be given to the possibility of such deficiencies in order that necessary substitution treatment may be applied.

Adrenal surgery has been greatly facilitated by the use of synthetic oxysteroids, and adequate amounts of adrenal hormone appear to control satisfactorily the severe postoperative adrenal insufficiency which follows removal of a functioning adrenal tumor associated with contralateral adrenal atrophy. Corticotropin therapy appeared to cause only temporary stimulation of the atrophic adrenal gland in such a case, with regression of adrenal function after cessation of treatment. It is suggested that there may exist a sustained impairment of endogenous corticotropin production in patients with Cushing's syndrome secondary to an adrenal tumor.

The truly specific application of corticotropin and steroid hormone therapy in the care of patients with endocrine deficiencies directly or indirectly involving the adrenal gland should significantly reduce mortality from operative procedures in this group of vulnerable patients.

ELECTROLYTE METABOLISM DURING RICE DIET

II. Serum Electrolytes in Patients with Severe Primary or Secondary Renal Disease

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AND
RUTH LOHMANN PESCHEL, M.D.
DURHAM, N. C.

IN A PREVIOUS paper,[1] a survey was given of the serum electrolyte pattern of patients on strict rice diet who had hypertensive vascular disease without advanced renal involvement. It was found that in 95% of these patients, serum electrolyte concentrations were well maintained. One should expect this to be different in patients with advanced kidney disease, and doubts are occasionally expressed whether or not salt restriction is applicable at all in such instances. The purpose of this paper is to report on the tolerance to rigid salt restriction in a series of patients with severe renal disease who were treated with the rice diet.

The presence of renal insufficiency greatly complicates the study and interpretation of chemical changes which take place in the body fluids as a result of dietary measures. Whereas in the previous group of patients a systematic approach was possible, determining the serum electrolytes at equal time intervals and under the influence of diets of identical composition, this procedure is not feasible for patients with definite renal insufficiency. Here modifications of the basic scheme of the diet, especially with regard to electrolyte intake, are frequently unavoidable. The point at which these modifications become necessary can hardly be predicted. Kempner,[2] therefore, considers the rice diet to be contraindicated unless frequent checks of the patient's blood chemistry are possible.

MATERIAL AND METHODS

The present series consisted of 80 patients chosen from those who were scheduled to start the rice diet treatment. The clinical diagnoses are listed in Table 1.

There were 55 males and 25 females. The ages ranged from 4 to 64, averaging 40 years. The patients were either hospitalized or ambulatory, in the latter case taking their meals under

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1. Peschel, E., and Lohmann-Peschel, R.: Electrolyte Metabolism During Rice Diet. I. Serum Electrolytes in Hypertensive Patients Without Evidence of Advanced Renal Involvement, A. M. A. Arch. Int. Med. **89**:234 (Feb.) 1952.

2. Kempner, W.: Treatment of Hypertensive Vascular Disease with Rice Diet, Am. J. Med. **4**:545 (April) 1948.

supervision. Adherence to the prescribed form of diet was currently checked by determining the urinary excretion of sodium and chloride, with simultaneous observation of the serum concentrations.

The majority of these patients had previously been treated elsewhere with some sodium chloride restriction, the degree of which could be estimated from the initial urinary electrolyte excretion. According to this criterion, 3 of the 80 patients had been on a rigid salt restriction

TABLE 1.—*Clinical Diagnoses*

Diagnosis			Patients, No.
I. Primary kidney disease			46
a. Chronic glomerulonephritis		33	
1. Nephrotic stage	8		
2. Hypertensive stage	25		
b. Kimmelstiel-Wilson syndrome		5	
c. Chronic pyelonephritis		4	
d. Polycystic kidney disease		4	
II. Secondary kidney disease			34
a. Arteriolonephrosclerosis		24	
b. Malignant hypertension		10	

TABLE 2.—*Initial Blood Nonprotein Nitrogen Values*

	Nonprotein Nitrogen	
Patients, No.	Range	Average
13	40 or below	33
27	41-60	48
17	61-80	74
5	81-100	88
15	101-200	135
3	Above 200	232

TABLE 3.—*Results of Phenolsulfonphthalein Tests*

	Total Excretion in 2 Hours, %	
Patients, No.	Range	Average
10	Above 40	52
16	30-39	34
17	20-29	24
13	10-19	15
6	5-9	7
18	Below 5	1

corresponding to that of the rice diet; 11 on a fairly marked restriction; 32 on moderate restriction, and 34 on a normal salt intake. For the purpose of this paper, all the 80 patients are considered as previously untreated, in order to apply the most rigid measure in regard to tolerance to the change in electrolyte intake.

Tables 2 and 3 indicate the degree of impairment of kidney function in the patients of this series. (In all instances in which the total phenolsulfonphthalein excretion in two hours was above 40%, there was an established history of chronic nephritis.) The average of the initial nonprotein nitrogen values of the 80 patients was 77 mg. per 100 cubic centimeters of blood; the average phenolsulfonphthalein excretion (total excretion in two hours) was 22%. Proteinuria was initially present in all 80 patients.

All patients were started on the strict rice diet without any modifications. This was continued for three months, or until the serum electrolyte determinations indicated major deviations from the values found to be average for patients with unimpaired renal regulatory function.[1] The electrolytes measured were sodium, potassium, chloride, and bicarbonate. Total base was determined in some instances, and in a number of patients the pH of the venous blood was also measured.

TABLE 4.—*Incidence of Serum Electrolyte Disturbance in 80 Patients with Renal Insufficiency on Rice Diet*

Patients with Serum Electrolyte Disturbance	None After 3 Mo.	After				Before Start of (Modified) Rice Diet
		3 Mo.	2 Mo.	1 Mo.	½ Mo.	
No.	36	6	15	14	6	3
%	45	7.5	18.8	17.5	7.5	3.7

TABLE 5.—*Relation of Serum Electrolyte Disturbance to Clinical Diagnosis*

	Serum Electrolyte Disturbance *					
	None After 3 Mo.	After				Before Start of (Modified) Rice Diet
		3 Mo.	2 Mo.	1 Mo.	½ Mo.	
Primary kidney disease	41.5	13	24	15	4.5	2
Secondary kidney disease	50	..	11.5	21	11.5	6
Chronic glomerulonephritis	40	16	26	13	5	..
Nephrotic stage	37	25	25	13	...	..
Kimmelstiel-Wilson syndrome	(40)	..	(60)	..	...	..
Chronic pyelonephritis	(75)	..	..	..	...	(25)
Polycystic kidney disease	(25)	..	(25)	(50)	...	..
Arteriolonephrosclerosis	67	..	8	12.5	12.5	..
Malignant hypertension	10	..	20	40	10	20

* Incidence in per cent of the respective group. The percentage figures have been put in parentheses when the total number of cases was less than eight.

TABLE 6.—*Relation of Serum Electrolyte Disturbance to Initial Blood Nonprotein Nitrogen and Phenolsulfonphthalein*

Serum Electrolyte Disturbance	Patients, No.	Average NPN, Mg./100 Cc.	Average PSP, Total Excretion in 2 Hr.
1. None after 3 mo.	36	61	29
2. After 3 mo.	6	52	28
3. After 2 mo.	15	77	21
4. After 1 mo.	14	121	14
5. After ½ mo.	6	72	14
6. Before start of rice diet	3	117	2

Technical details of the procedures were the same as described in the previous paper,[1] except for the time intervals between the tests, which, in this series, varied from patient to patient, depending on clinical indications and the outcome of previous electrolyte determinations.

RESULTS

In order to arrive at a somewhat quantitative estimation of the tolerance to rigid restriction of sodium chloride intake in patients with impaired renal function, we have grouped the patients of this series according to the length of time they were given the strict rice diet before major disturbances of the serum electrolyte equilibrium occurred (Table 4). One or more of the following criteria were con-

sidered major disturbances: serum sodium concentration below 130 mEq per liter, potassium concentration above 6.5 mEq per liter, and chloride concentration below 85 mEq per liter. Such a definition of "major disturbance" is necessarily arbitrary, both in a general sense and with regard to the clinical importance in the individual case.

In Table 5, serum electrolyte regulation has been correlated with clinical diagnoses. Table 6 lists the relations of serum electrolyte disturbance to initial blood nonprotein nitrogen and to phenolsulfonphthalein excretion.

Total base determinations showed that the difference between serum total base and sodium concentrations is not altered in cases of low serum sodium; it averaged 11.5 mEq per liter in 15 patients with a low (average 124.8 mEq per liter) serum sodium concentration as compared with 11.7 mEq per liter in 80 patients with a normal (average 142.3 mEq per liter) serum sodium concentration. This shows again that changes in serum sodium concentration indicate corresponding changes in total ionic concentration and tonicity.

Determinations of pH on venous blood and measurements of serum bicarbonate showed the picture to be similar to that in the group of hypertensive patients without major renal involvement,[1] if patients in the last two or three days of terminal renal failure are excluded. Except for those, there was no instance of uncompensated acidosis. Nor did compensated acidosis occur except in the last days of life. Bicarbonate measurements in the present series of patients before starting the rice diet and after 5, 10, and 15 weeks on the rice diet showed averages of 26.6, 31.7, 33.2, and 32.0 mEq per liter respectively.

COMMENT

Of the amount contained in the glomerular filtrate, 99.566% is reabsorbed in a person on a normal mixed diet [3] and 99.997% in a person on rice diet. The figures are similar in regard to chloride. Calculated on this basis, a small change in reabsorption could have far-reaching consequences; if other factors remained unchanged, a 0.1% reduction of reabsorptive capacity would increase the 24-hour urinary sodium excretion of a patient on rice diet from 0.5 mEq to 25.5 mEq. Other factors, such as glomerular filtration rate, will not remain unchanged in the conditions under consideration. But even if the glomerular filtration rate would be decreased by 50%, the 0.1% reduction of reabsorptive capacity would increase the daily urinary sodium loss of the rice diet patient to 13 mEq. That means, in terms of sodium chloride, that the minute reduction in sodium reabsorption of 0.1% would cause a daily loss of 0.75 gm. of sodium chloride, about three times as much as the total daily intake of a patient on rice diet. Considering this, it should be anticipated theoretically that with a severely damaged kidney serum electrolyte concentrations could never be maintained when sodium and chloride intake are extremely restricted over an extended period, whether the insufficient sodium reabsorption is primary, or secondary to diminished ammonia production, and whether it is irreversible or reversible.[4]

3. Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, Cambridge, Mass., Harvard University Press, 1947.

4. Kempner, W.: Anoxemia of the Kidney as Cause of Uremic Acidosis: Inhibitory Effect of Low Oxygen Tension on the Deamination of Aminoacids in Kidney Tissue, Am. J. Physiol. **123**:117 (July) 1938.

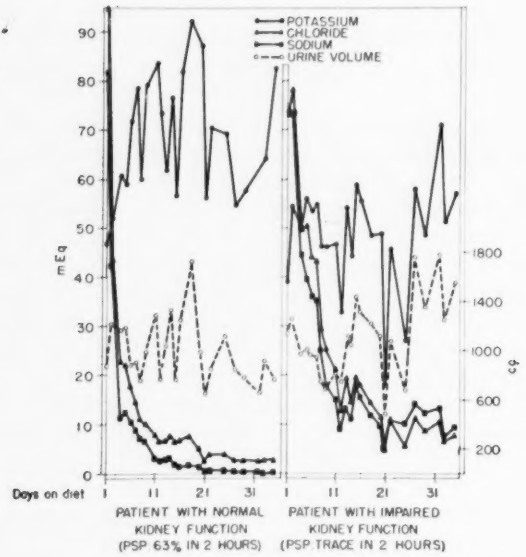

Chart 1.—Urinary electrolyte excretion (mEq. in 24 hours) in first five weeks on rice diet.

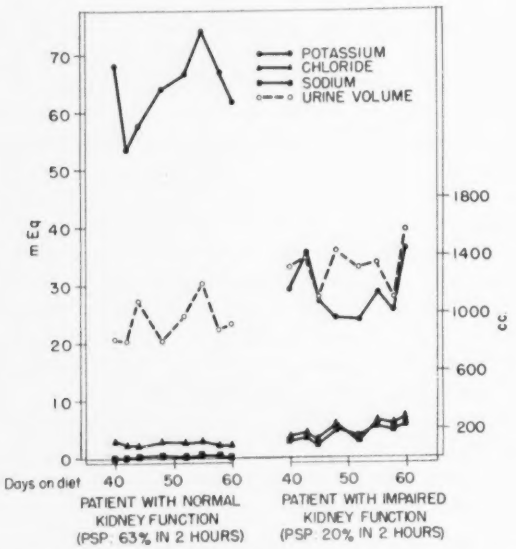

Chart 2.—Urinary electrolyte excretion (mEq. in 24 hours) after 40 days on rice diet.

Practically, the urinary losses of sodium and chloride are smaller than would be expected from the theoretical considerations set forth above. Charts 1 and 2 illustrate with representative examples the renal electrolyte conservation on strict rice diet in patients with severe kidney disease as compared with that of patients with unimpaired renal regulatory function. With the same intake, patients with severe renal disease excrete more sodium and chloride and less potassium, and it might be noted that, as a consequence of the loss of functional elasticity of the kidney, the fluctuations in the daily excretion of the single electrolytes parallel each other to a certain degree, all being influenced by the 24-hour urine volume (compare the 12th to 15th and 21st to 35th days in Chart 1).

If one agrees that therapeutically the most rigid salt restriction compatible with the individual condition is desirable, then it is of importance to know when, approximately, a severe serum electrolyte disturbance is to be expected, whether there is a criterion for predicting its occurrence, and when and in what amounts modifications should be introduced.

As to the patients studied in this series, it is remarkable that serum electrolyte equilibrium was satisfactorily maintained in 45%. This group of 36 patients could be treated as if they had completely normal renal regulatory capacity, although an average initial nonprotein nitrogen of 61 mg. per 100 cubic centimeters of blood and an average phenolsulfonphthalein excretion of 29% in two hours indicated the severity of impairment of renal function. These patients did not receive any modification of the strict rice diet for three to four months; after that time, slight additions were started in each instance, amounting, in terms of sodium chloride intake, to 2 to 4 mEq. per day. Further serum electrolyte determinations were done after an additional period of two to three months and from then on in varying intervals up to a total observation period of several years. In 12 of the 36 patients a major electrolyte disturbance developed later, after additional periods of 2 to 17 (average 6) months; it was compensated by increased modifications. Twenty-four of the 36 patients went along satisfactorily on the same type and amount of additional food as was given to patients without renal involvement.

Three patients showed a serum electrolyte disturbance at the initial examination prior to the scheduled start of the rice diet treatment. None of them belonged in the group of patients who had been treated previously with a marked or fairly marked restriction of sodium chloride intake. This emphasizes again that the natural course of severe kidney disease itself includes the tendency toward electrolyte derangement, a factor which might be involved in other cases of this series too.

In 55% of the 80 patients of this series, a major serum electrolyte disturbance developed within four months. A classification according to the underlying disease (Table 5) shows that the tolerance to the rigid restriction of sodium chloride intake is not distinctly correlated with the nature of the processes which led to the renal insufficiency. A larger number of observations might confirm a better tolerance in cases of arteriolonephrosclerosis and chronic pyelonephritis. In the nephrotic stage of chronic glomerulonephritis, as in cases with cardiac edema, an additional electrolyte supply can occur when a mobilization of the edema fluid has been achieved and when, of its contents, more water than electrolytes is excreted in the urine.

Table 6 shows that the degree of azotemia is a relatively unreliable guide for predicting the occurrence of serum electrolyte disturbance on strict rice diet. There is a correlation with the result of the phenolsulfonphthalein test which, at first

glance, seems to be rather close. The lower the phenolsulfonphthalein excretion the earlier one should expect a major disturbance in the electrolyte equilibrium. However, in this series at least, statistical significance can be attributed only to Groups 4 and 6 as compared with Group 1, P being less than 0.01 for Group 4 and about 0.02 for Group 6 but above 0.05 for the other Groups.

Clinically, the serum electrolyte disturbance, if sufficiently pronounced, usually manifested more or less the well-known features of the low salt syndrome.[5] Symptoms suggesting electrolyte derangement are occasionally seen with serum sodium or chloride values higher than 130 or 85 mEq per liter, respectively. On the other hand, there are patients who seem to establish a new equilibrium at a sodium level of as low as 120 mEq per liter without directly apparent clinical consequences. In a few of the cases studied, hyperpotassemia with or without the typical electrocardiogram changes was found when there was no simultaneous hyponatremia or hypochloremia of similar degree.

The low salt syndrome progressed only rarely to the critical picture of peripheral vascular collapse and renal shutdown with oliguria or anuria; in most instances, it was possible to correct it in time by modification of the diet, consisting of sodium chloride administration. In terminal phases, it was sometimes impossible to repair the electrolyte derangement. Usually, even in patients with extremely low kidney function, one can compensate the deficiency in renal electrolyte conservation by astonishingly small additions if they are given early enough. These additions, still keeping the diet well within the range of a very low sodium diet, might consist of vegetables, for example, celery (100 gm. of raw celery contains about 0.3 gm. of sodium chloride) or of regular bread (one slice contains approximately 0.2 gm. of sodium chloride), or, if the deficit is severer, sodium chloride may be given parenterally, preferably in hypertonic solution, since the disturbance is usually that of a hypotonic dehydration. It seems preferable for this type of patient to give the amount of salt which is considered necessary to repair the electrolyte equilibrium in small and repeated portions rather than in massive doses, in order to forestall pulmonary edema. Additions containing sodium chloride should be supplied as soon as a major electrolyte disturbance arises because only early replacement of the salt deficit maintains or restores efficient cardiovascular function and prevents the vicious circle: renal disease → serum electrolyte disturbance → peripheral circulatory insufficiency → prolonged renal vasoconstriction → additional kidney damage.

5. McCance, R. A.: Experimental Sodium Chloride Deficiency in Man, Proc. Roy. Soc., London, s.B **119**:245 (Feb. 1) 1936. Thorn, G. W.; Koepf, G. F., and Clinton, M., Jr.: Renal Failure Simulating Adrenocortical Insufficiency, New England J. Med. **231**:76 (July 20) 1944. Danowski, T. S.; Winkler, A. W., and Peters, J. P.: Salt Depletion, Peripheral Vascular Collapse, and the Treatment of Diabetic Acidosis, Yale J. Biol. & Med. **18**:405 (May) 1946. Elkinton, J. R.; Danowski, T. S., and Winkler, A. W.: Hemodynamic Changes in Salt Depletion and in Dehydration, J. Clin. Invest. **25**:120 (Jan.) 1946. Marriott, H. L.: Water and Salt Depletion (Croonian Lectures), Brit. M. J. **1**:245 (Feb. 15) 1947; **1**:285 (March 8) 1947; **1**:328 (March 15) 1947. Soloff, L. A., and Zatuchni, J.: Syndrome of Salt Depletion: Induced by a Regimen of Sodium Restriction and Sodium Diuresis, J. A. M. A. **139**:1136 (April 23) 1949. Schroeder, H. A.: Renal Failure Associated with Low Extracellular Sodium Chloride: Low Salt Syndrome, ibid. **141**:117 (Sept. 10) 1949. Nickel, J. F.; Lowrance, P., and Leifer, E.: Effect of Sodium Depletion and Repletion on Renal Function and Body Fluids During Uremia, abstracted, J. Clin. Invest. **30**:664 (June) 1951.

SUMMARY AND CONCLUSIONS

A study was made on 80 patients with severe primary or secondary kidney disease in regard to the tolerance to a rigid restriction of sodium chloride intake, as in the rice diet. The degree of impairment of kidney function was characterized by an average initial blood nonprotein nitrogen of 77 mg. per 100 cubic centimeters and an average phenolsulfonphthalein excretion (total in two hours) of 22%. The serum electrolytes sodium, potassium, chloride, and bicarbonate and, in some instances, total base or blood pH were determined at monthly or shorter intervals. All patients were maintained on the strict rice diet until the serum electrolyte determinations indicated major deviations. The period of time on strict rice diet until such major electrolyte disturbances developed was used as a criterion for the tolerance to the rigid restriction of sodium chloride intake.

Contrary to what would be expected on the basis of theoretical considerations, advanced renal disease allows maintenance of serum electrolyte concentrations in a considerable number of patients when their sodium and chloride intake are extremely restricted over an extended period. It was found that in this series of patients 45% did not show a major electrolyte disturbance after three months on strict diet, 7.5% showed it after three months, 18.8% after two months, 17.5% after one month, and 7.5% after half a month; 3.7% were in major electrolyte imbalance before the diet (in modified form) was started.

There was no distinct correlation of these findings with the nature of the processes which led to the renal insufficiency. The degree of azotemia was a relatively unreliable guide for predicting the occurrence of serum electrolyte disturbance, whereas there was a correlation with the result of the phenolsulfonphthalein test.

The deficiency in renal electrolyte conservation could be compensated by astonishingly small additions of sodium chloride if these were given early enough so that even with the modifications the diet could be kept well within the range of a very low sodium diet.

Acidosis did not occur (except during the last days of life, in some instances), although the general clinical state of many of these patients would have led one to expect its presence. The composition of the rice diet helps to reduce the production of acid radicals and favors the formation of bicarbonate reserve.

The strict rice diet can be given to patients with the most severely impaired kidney function, but checks of the serum electrolytes have to be done at at least biweekly intervals, more frequently, of course, if a disturbance has been found or if clinical indications suggest it. The lower the result of the phenolsulfonphthalein test, the earlier one must expect a major disturbance in the electrolyte equilibrium.

INHIBITORY EFFECTS OF PORTAL CIRRHOSIS OF LIVER ON PROSTATIC ENLARGEMENT

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BENIGN prostatic hypertrophy is a very common disease in men over 50 years of age,[1] but little is known of the precise cause of this disorder. Various theories have been promulgated, but most of them have been untenable. Today most authorities believe that the cause may be hormonal imbalance.

There is abundant evidence that cirrhosis of the liver is often accompanied by hormonal abnormalities. Testicular atrophy, loss of body hair, change in pubic hair distribution, loss of libido, and, at times, gynecomastia have been described in cases of hepatic cirrhosis.[2] It is thought by many that these are secondary changes, caused by the inability of the damaged liver to metabolize estrogenic hormones properly.[3] Whether the derangement of hepatic physiology involves other hormones is not clearly established, but various investigators believe that factors such as pituitary, adrenal, and testicular function deserve consideration.[4]

No direct evidence has been presented to suggest that the presence of cirrhosis causes a reduction of the incidence of prostatic hypertrophy. Bennett, Baggenstoss, and Butt [5] reported a lower incidence of hypertrophy in patients with cirrhosis in

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1. (*a*) Moore, R. A.: Benign Hypertrophy of the Prostate: A Morphological Study, J. Urol. **50**:680-710, 1943. (*b*) Anderson, W. A. D., editor: Pathology, St. Louis, C. V. Mosby Company, 1948.

2. Lloyd, C. W., and Williams, R. H.: Endocrine Changes Associated with Laennec's Cirrhosis of the Liver, Am. J. Med. **4**:315-330, 1948.

3. Paschkis, K. E., and Rakoff, A. E.: Some Aspects of the Physiology of Estrogenic Hormones in Recent Progress in Hormone Research: The Proceedings of the Laurentian Hormonal Conference, Vol. 5, edited by G. Pincus, New York, Academic Press, Inc., 1950, p. 115. Zondek, B.: Studi sperimentali e clinici sul meccanismo di azione ed inattivazione dell' ormone estrogeno, Minerva ginec. **3**:188-192, 1951. Glass, S. J.; Edmondson, H. A., and Soll, S. N.: Sex Hormone Changes Associated with Liver Disease, Endocrinology **27**:749-752, 1940.

4. Lynch, K. M., Jr.: Does the Sertoli Cell Produce Estrogen? S. Forum (1950), pp. 550-556, 1951. Williams, T. L.; Cantarow, A.; Paschkis, K. E., and Havens, W. P., Jr.: Urinary 17-Ketosteroids in Chronic Liver Disease, Endocrinology **48**:651-657, 1951. Huggins, C.: The Etiology of Benign Prostatic Hypertrophy, Bull. New York Acad. Med. **23**:696-704, 1947. Lowsley, O. S., and Kirwin, T. J.: Clinical Urology, Ed. 2, Baltimore, Williams & Wilkins Company, 1944, Vol. 1, pp. 826-832. Anderson.[1b]

5. Bennett, H. S.; Baggenstoss, A. H., and Butt, H. R.: The Testis, Breast and Prostate of Men Who Die of Cirrhosis of the Liver, Am. J. Clin. Path. **20**:814-828, 1950.

their 51-to-60-year-old group but found no difference in the incidence of prostatic enlargement between those with and those without cirrhosis in the other two age groups, 50 years or less, and 61 years or more. They attributed the difference in the 51-to-60-year-old group largely to the fact that most of their controls without cirrhosis, fell into an older age group. Wu [6] found a lower incidence of gross enlargement but a higher incidence of microscopic hyperplasia of the prostate in patients with cirrhosis. Both of these series were small, however, and many of the patients with cirrhosis in the series reported by Bennett were 50 years of age or less. Relatively little prostatic enlargement occurs before the age of 50 years either in those who have cirrhosis or in those who do not.

It is possible that if a sufficiently large series were studied and the age factor considered, a correlation between the incidences of the two diseases might be found.

At Bellevue Hospital many chronic alcoholics with portal cirrhosis are admitted each year. Because of the insidious nature of the onset of portal cirrhosis and the unreliability of these patients, it is impossible to determine the duration of the illness in each case. The present study is based on autopsy material from 333 white men with cirrhosis and 359 without, used as controls. Both series included only men 50 years of age and over. All were from a series of 18,000 autopsies performed in 1935-1951. The observations and conclusions in this report are based on the gross and histologic findings.

The majority of these men with cirrhosis were chronic alcoholics, and the conclusions may not apply to patients with portal cirrhosis not associated with excessive alcohol intake. The controls were picked at random from a series of white men, 50 years of age or over, who did not have liver disease or known endocrine dysfunction. Many of the controls had chronic debilitating diseases, so the influence of possible differences in the state of general nutrition tends to be minimized. No attempt was made to exclude chronic alcoholics in the control group.

CRITERIA

The criteria used to determine hypertrophy of the prostate were as follows:

A. Gross
   1. Size (over 5 cm. or 2 in. in transverse diameter)
   2. Asymmetry
   3. Nodularity
   4. Prominence of medial lobe
   5. Dilatation and hypertrophy of the urinary bladder (hydroureter and hydronephrosis if present)

B. Histologic
   1. Nodular grouping of acini with compression of adjacent tissue
   2. Myomatous nodules
   3. Papillary infoldings and "bridging" of glandular epithelium
   4. Predominance of glandular tissue
   5. Scarcity of corpora amylacea

On the basis of the above criteria, the prostatic hypertrophy was graded as none, mild, moderate, or severe (Tables 1 and 2). In addition, the degree of portal

6. Wu, S. D.: Anatomic Changes in the Prostate of Patients with Cirrhosis of the Liver, Arch. Path. **34**:735-741, 1942.

cirrhosis was established morphologically by consulting the protocols and reviewing the slides of the liver. All cases of biliary, syphilitic, cardiac, pigmentary, and parasitic cirrhosis were excluded from this study. Cases of very mild or questionable cirrhosis were also excluded. The remaining cases were graded as mild or severe (Tables 1 and 2). In evaluating the degree of prostatic hypertrophy,

TABLE 1.—*The Relation of Portal Cirrhosis of the Liver to Gross Enlargement of the Prostate*

Gross Enlargement, Prostate		None		Mild		Moderate		Severe		Total Enlarged		Moderate and Severe Enlargement		Total Cases
Age Group		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
50-59	Controls	59	66	18	20	10	11	3	3	31	34	13	14	90
	Mild cirrhosis	29	66	12	27	3	7	..	..	15	34	3	7	44
	Severe cirrhosis	74	80	15	16	4	4	..	..	19	20	4	4	93
60-69	Controls	58	43	31	23	35	26	10	8	76	57	45	34	134
	Mild cirrhosis	35	66	11	21	6	11	1	2	18	34	7	13	53
	Severe cirrhosis	63	79	12	15	5	6	..	..	17	21	5	6	80
70-79	Controls	44	41	28	26	20	19	15	4	63	59	35	33	107
	Mild cirrhosis	12	55	3	14	5	23	2	8	10	45	7	31	22
	Severe cirrhosis	16	53	9	30	4	13	1	4	14	47	5	17	30
80 and over	Controls	6	21	7	25	9	32	6	22	22	79	15	54	28
	Mild cirrhosis	2	28.5	3	43	..	..	2	28.5	5	71.5	2	28.5	7
	Severe cirrhosis	1	25	..	..	3	75	..	..	3	75	3	75	4
Total, all ages	Controls	167	47	84	23	74	21	34	9	192	53	108	30	359
	Mild cirrhosis	78	62	29	23	14	11	5	4	48	38	19	15	126
	Severe cirrhosis	154	74	36	17.5	16	8	1	0.5	53	26	17	8	207
	All cirrhotics	232	70	65	19	30	9	6	2	101	30	36	11	333

TABLE 2.—*The Relation of Portal Cirrhosis of the Liver to Microscopic Hyperplasia of the Prostate*

Microscopic Hyperplasia, Prostate		None		Mild		Moderate		Severe		Total Hyperplastic		Moderate and Severe Hyperplasia		Total Cases*
Age Group		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
50-59	Controls	19	22	41	47	21	24	6	7	68	78	27	31	87
	Mild cirrhosis	16	49	13	39	4	12	..	..	17	51	4	12	33
	Severe cirrhosis	21	32	33	50	12	18	..	..	55	68	12	18	66
60-69	Controls	21	17	50	40	33	26	21	17	104	83	54	43	125
	Mild cirrhosis	12	26	23	50	9	20	2	4	34	74	11	24	46
	Severe cirrhosis	28	50	22	39	5	9	1	2	28	50	6	11	56
70-79	Controls	24	23	37	35	30	28	15	14	82	77	45	42	106
	Mild cirrhosis	5	26	3	16	8	42	3	16	14	74	11	58	19
	Severe cirrhosis	7	26	14	52	6	22	..	..	20	74	6	22	27
80 and over	Controls	1	4	12	44	8	30	6	22	26	96	14	52	27
	Mild cirrhosis	1	17	4	67	..	..	1	17	5	83	1	17	6
	Severe cirrhosis	..	..	2	67	1	33	..	..	3	100	1	33	3
Total, all age groups	Controls	65	19	140	40	92	26	48	15	280	81	140	41	345
	Mild cirrhosis	34	33	43	41	21	20	6	6	70	67	27	26	104
	Severe cirrhosis	56	37	71	47	24	16	1	1	96	63	25	17	152
	All with cirrhosis	90	35	114	45	45	18	7	2	166	65	52	20	256

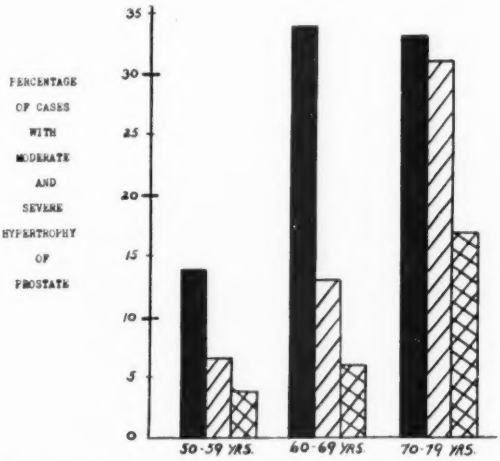
* In some cases slides were not available; hence the difference in the number of cases in Tables 1 and 2.

emphasis was placed on the gross rather than the histologic findings because in most of the cases only a single histologic preparation of the prostate was available and this may not have been from a representative portion of the gland.

FINDINGS

The results are presented in the two tables and in the chart. The total incidence of gross prostatic enlargement is almost twice as high in the men without cirrhosis (53%) as in those with cirrhosis (30%). The incidence of benign prostatic hypertrophy in those without cirrhosis is similar to that reported in the literature. Various

authors give incidences of prostatic hypertrophy ranging from about 50 to 60% in unselected white men over 50 years of age.[7] The combined incidence of moderate and severe gross enlargement is almost four times as high in the controls (30%) as in those with severe cirrhosis (8%) in the present series. This difference is statistically significant (using the χ-square test, P is less than 0.05). There is some indication not only that the incidence of moderate and severe hypertrophy is lower but that the age of onset may be delayed in men with cirrhosis. The incidence of moderate and severe hypertrophy in those with severe cirrhosis is strikingly low (6%) between the ages of 50 and 69 years as compared with 28% in the controls in the same age group. The histologic findings are similar but less striking. The difference in the 70- to 79-year age groups is not as great, either grossly or histologically. Thus, it would appear that the presence of severe cirrhosis may postpone the onset of marked enlargement of the prostate.



Gross hypertrophy of prostate. Black bar indicates cases without cirrhosis; hatched bar, cases with mild cirrhosis, and cross hatched bar, cases with severe cirrhosis.

Histologically the incidence of all degrees of hyperplasia taken together is not very much greater than in the controls, but here, too, the incidence of moderate and severe hyperplasia is significantly higher in the cases without cirrhosis, particularly when they are compared with those with severe cirrhosis (Tables 1 and 2, Totals, All Age Groups).

Similar and even more striking differences are noted in most of the individual age groups, the cases of mild cirrhosis usually occupying an intermediate position between the noncirrhotic cases and those with severe cirrhosis. The age group of 80 years and over is considered to be too small for proper statistical evaluation.

7. Socin, A., and Burckhardt, E.: Die Verletzungen und Krankheiten der Prostata, Stuttgart, F. Enke, 1902, p. 53. Randall, A.: Surgical Pathology of Prostatic Obstructions, Baltimore, Williams & Wilkins Company, 1931. Krogius, A.: Studien über die Natur der sogenannten Prostatahypertrophie, Acta chir. scandinav. **72**:47-78, 1932. Moore, R. A.: The Morphology of Small Prostatic Carcinoma, J. Urol. **33**:224-234, 1935. Moore.[1a]

As confirmatory evidence of the degree of prostatic hypertrophy it is significant that hypertrophy of the urinary bladder wall was twice as common and hydroureter and hydronephrosis four times as common in the noncirrhotic patients as in those with varying degrees of cirrhosis of the liver.

In the majority of cases gross enlargement of the prostate was accompanied by histologic hyperplasia. However, in a significant number of cases there was no correlation. No distinctive differences were noted in the histologic nature of hyperplasia in those with and those without cirrhosis. Myomatous nodules apparently occurred with equal frequency in the enlarged glands of both the patients with cirrhosis and the controls.[1a]

In order to determine whether the presence of cirrhosis retards the development of processes other than the hypertrophy of the prostate, a comparison of malignant tumors in general was made in the group with cirrhosis and the control group. The incidence of carcinoma of the prostate was approximately 7% in those without cirrhosis as compared with 5% in the cirrhotic men. In each group about one-half of the cases of malignant tumor were recognized only by histologic examination. It is possible that if more sections of the prostate were available, a higher incidence might have been found. The incidence of carcinoma of the liver in those with severe cirrhosis was about 10%, or about double that usually quoted for cirrhotic patients in general.[1b] Malignant hepatomas accounted for one-half of all cases of malignant disease in this group, carcinoma of the lung and of the stomach being next in frequency, with an incidence of about 2% each. Among those without cirrhosis carcinoma of the lung, with an incidence of 9%, constituted about one-third of all malignant tumors found. Malignant tumors of the alimentary tract made up another third in this group. Except for the high incidence of liver cancer in the cirrhotic patients and the large number of lung cancers in the controls, the frequency of various diseases was about the same in each group.

COMMENT

It is possible that the high mortality in men with cirrhosis before the age of 50 years [8] makes the group studied here a select one. It may be, therefore, that those with cirrhosis who are older than 50 years are not representative of all cirrhotic men. However, the finding that the incidence of carcinoma of the prostate and of other organs is not lower in cirrhotic men than in noncirrhotic men suggests that the two groups are comparable and that the difference in the incidence of prostatic hypertrophy is significant.

One can at best only speculate as to why there is a lowered incidence of prostatic hypertrophy in men with cirrhosis. The condition is not necessarily hormonal in nature, yet the fact that estrogens are not properly activated in liver disease suggests that these may be involved. There is considerable evidence that the capacity of the damaged liver to neutralize estrogenic substances is impaired. It may be that an increase of the level of circulating free estrogenic substances over a prolonged period, as may possibly occur in chronic liver disease, helps prevent or retards glandular hyperplasia of the prostate, particularly marked hyperplasia. Peirson's

8. Harrison, T. R., and others, editors: Principles of Internal Medicine, Philadelphia, The Blakiston Company, 1950, pp. 1481-1486.

9. Peirson, E. L.: A Study of the Effect of Stilbestrol Therapy on the Size of the Benignly Hypertrophied Prostate Gland, J. Urol. **55**:73-78, 1946.

findings [9] suggest that a reduction of the size of the enlarged prostate can be produced with diethylstilbestrol, though admittedly the series he reported was small. However, more recent work indicates that the role of the human liver in estrogen inactivation is less impressive.[10]

Some authors claim that estrogens cause proliferation of the stroma with the formation of myomatous nodules and a reduction of glandular hyperplasia, and that androgens have the opposite effect.[11] Nevertheless, proliferations of the two elements are usually found together,[1a] as it was in both groups of this study. Others postulate an alteration in the testis-pituitary relationship and believe that testicular atrophy, as occurs in aging, causes a reduction of pituitary inhibition with resultant excess production of androgenic substances by the hypophysis. This in turn, it is claimed, causes prostatic hyperplasia.[1b] If this were the mechanism involved, one might expect a higher incidence of enlargement of the prostate in men with cirrhosis, for testicular atrophy is often noted in this disorder. Further evidence that the testes may be concerned in prostatic hypertrophy is found in the fact that no prostatic enlargement occurs if the testes fail to develop or if they are removed before puberty.[12] However, castration after the prostate has enlarged apparently causes no reduction of its size.[13]

SUMMARY

The prostates of 333 men with cirrhosis, aged 50 years and over, and those of a similar number of controls of the same age were compared as to the degree of hypertrophy. There is a lower incidence of significant hypertrophy of the prostate in men with cirrhosis. Moreover, not only is the incidence less but the age of onset of hypertrophy in cirrhotic patients is delayed as compared with the control group. The difference is accentuated if only cases of moderate and severe hypertrophy are compared. While the exact nature of this relationship cannot be determined, it is suggested that protractedly elevated estrogen levels or other hormonal imbalance may be responsible for the lower incidence of prostatic hypertrophy in cases of portal cirrhosis of the liver.

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13. Anderson.[1b] Bell.[12]

HEMATOLOGIC STUDIES OF IRRADIATED SURVIVORS IN HIROSHIMA, JAPAN

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THE IMMEDIATE effects of radiation injury upon the hemopoietic system are well known, but few such observations have been made on humans surviving a single massive exposure. Snell, Neel, and Ishibashi [1] initiated such a controlled study in 1947 on a group of subjects exposed to radiation by the atomic bombing of Hiroshima on Aug. 6, 1945.

The present report is a hematologic survey of similar nature conducted from March, 1948, to February, 1949, on 824 irradiated subjects, residents of Hiroshima, and 1,145 control subjects, residents of Kure. The studies reported on 304 of the irradiated subjects represent a second examination, as the initial examination was included in the report in 1947.[1] It represents a study of the hematologic effects of radiation 33 to 44 months after the explosion of the atomic bomb.

It is felt that no useful purpose will be served by a review of the literature concerning the effects of radiation injury on the hemopoietic tissues. Snell and his associates [1] conclude from their observations made from 20 to 33 months after the detonation of the atomic bomb that in view of the great medical and civil disruption in Hiroshima after the bombing, caution must be exercised in attributing the slight recorded [hematological] differences to the atomic bombing, although it seems possible that irradiation was, to some extent, responsible.[1]

METHODS

Methods of case selection, examination of patients, laboratory methods, and statistical analysis were identical to those employed by Snell and his associates.[1] in their earlier report. In brief, irradiated subjects fulfilling the criterion of epilation were selected at random; a control group, residents of Kure, was selected by similarity of age and sex to the exposed group. Results were compared not only in terms of the mean values for the two populations but also in terms of the

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This paper is presented as one of a series of hematologic studies of the survivors in Hiroshima and Nagasaki, who were exposed to short-wave radiation of the atomic explosions. It follows in sequence the study by G. LeRoy (Hematology of Atomic Bomb Casualties, Arch. Int. Med. **86**:691-710 [Nov.] 1950) and that by Snell, Neel, and Ishibashi. It precedes, however, the paper by J. H. Folley, W. Borges, and T. Yamawaki (Incidence of Leukemia in Survivors of the Atomic Bomb in Hiroshima and Nagasaki, Japan, Am. J. Med. **13**:311-321 [Sept.] 1952), which deals with the same group after the appearance of leukemia.

1. Snell, F. M.; Neel, J. V., and Ishibashi, K.: Arch. Int. Med. **84**:569, 1949.

TABLE 1.—*Hematologic Values for Exposed and Control Subjects for 1948-1949 Compared with Similar Data for 1947-1948* *

Observation	Year	Control Subjects			Exposed Subjects			Difference ± Error of Difference	*t* Value	*f* Value	No. of Pairs	Mean Difference S. E.	*t* Value
		No.	Mean ± S. E.	S. D.	No.	Mean ± S. E.	S. D.						
Red blood cell count	1947-48	709	4,604,000 ±17,000	±442,000	629	4,521,000 ±20,000	±501,000	+83,000 ±26,000	3.2	1.29	437	+65,000 ±27,000	2.4
	1948-49	1,108	4,390,000 ±11,600	±385,000	814	4,296,800 ±14,000	±400,000	+91,200 ±18,200	5.0	1.08	702	+49,100 ±17,800	2.7
Hemoglobin, gm./100 cc.	1947-48	912	13.14 ±0.041	±1.25	872	12.84 ±0.046	±1.34	+0.30 ±0.061	4.9	1.15	447	+0.26 ±0.075	3.5
	1948-49	1,105	12.73 ±0.032	±1.078	814	12.64 ±0.042	±1.210	+0.09 ±0.053	1.5	1.26	702	+0.15 ±0.179	0.8
Hematocrit reading, %	1947-48	802	41.46 ±0.13	±3.69	757	40.98 ±0.14	±3.73	+0.48 ±0.19	2.5	1.08	...	.....	...
	1948-49	1,106	39.61 ±0.089	±2.96	814	38.93 ±0.116	±3.33	+0.68 ±0.147	4.6	1.26	702	+0.62 ±0.148	4.2
Mean corpuscular volume	1947-48	629	87.85 ±0.28	±6.90	546	88.34 ±0.30	±7.26	−0.49 ±0.41	1.2	1.11	...	.....	...
	1948-49	1,105	90.49 ±0.169	±5.63	814	90.93 ±0.22	±6.28	−0.44 ±0.277	1.6	1.24	704	+0.22 ±0.267	0.8
Mean corpuscular hemoglobin	1947-48	708	28.74 ±0.088	±2.34	627	28.55 ±0.10	±2.59	+0.19 ±0.16	1.2	1.23	433	+0.21 ±0.13	1.6
	1948-49	1,104	29.06 ±0.064	±2.135	814	29.48 ±0.079	±2.965	−0.42 ±0.102	4.0	1.13	702	−0.021 ±0.107	0.2
Mean corpuscular hemoglobin concentration	1947-48	665	32.15 ±0.053	±1.37	757	32.20 ±0.052	±1.43	−0.05 ±0.074	0.7	1.09	...	.....	...
	1948-49	1,104	32.11 ±0.040	±1.332	814	32.42 ±0.048	±1.392	−0.31 ±0.063	4.8	1.09	702	−0.11 ±0.074	1.5
Plasma protein, gm./100 cc.	1947-48	912	7.59 ±0.017	±0.500	872	7.65 ±0.019	±0.549	−0.06 ±0.025	2.4	1.21	443	−0.021 ±0.028	0.3
	1948-49	1,110	7.43 ±0.015	±0.522	814	7.39 ±0.019	±0.554	+0.04 ±0.025	1.9	1.13	702	+0.05 ±0.025	2.0

TABLE 1.—*Hematologic Values for Exposed and Control Subjects for 1948-1949 Compared with Similar Data for 1947-1948* *—*Continued*

Observation	Year	Control Subjects			Exposed Subjects			Difference ± Error of Difference	*t* Value	*f* Value	No. of Pairs	Mean Difference S. E.	*t* Value
		No.	Mean ± S. E.	S. D.	No.	Mean ± S. E.	S. D.						
White blood cell count	1947-48	707	9,903 ±101	±2,693	645	9,847 ±122	±3,100	+56 ±160	0.6	1.32	455	+20 ±170	0.1
	1948-49	1,096	9,476 ±77	±2,565	824	9,605 ±112	±3,240	−129 ±137	0.9	1.6	713	−148 ±159	0.9
Neutrophiles, %	1947-48	707	54.96 ±0.35	±9.35	637	54.96 ±0.39	±9.94	0.00 ±0.53	0.0	1.13	432	−0.59 ±0.64	0.9
	1948-49	1,112	53.48 ±0.342	±11.4	815	53.37 ±0.406	±11.60	+0.11 ±0.530	0.2	1.03	707	+0.51 ±0.59	0.8
Lymphocytes, %	1947-48	707	29.40 ±0.28	±7.54	637	28.01 ±0.31	±7.89	+1.39 ±0.42	3.3	1.10	432	+2.02 ±0.48	4.2
	1948-49	1,112	29.10 ±0.261	±8.72	815	28.66 ±0.302	±8.66	+0.44 ±0.400	1.1	1.01	707	+0.44 ±0.438	1.0
Monocytes, %	1947-48	707	6.36 ±0.085	±2.26	637	6.33 ±0.093	±2.35	+0.03 ±0.13	0.2	1.08	432	+0.02 ±0.14	0.1
	1948-49	1,112	7.00 ±0.087	±2.90	815	6.68 ±0.109	±3.11	+0.32 ±0.139	2.3	1.15	707	+0.14 ±0.168	0.8
Eosinophiles, %	1947-48	707	8.93 ±0.26	±7.02	637	10.76 ±0.32	±7.97	−1.83 ±0.41	4.5	1.29	432	−0.99 ±0.47	2.1
	1948-49	1,112	10.39 ±0.26	±8.66	815	11.63 ±0.34	±9.96	−1.24 ±0.434	2.8	1.32	707	−1.26 ±0.512	2.4
Basophiles, %	1948-49	1,112	0.91 ±0.023	±0.775	815	0.81 ±0.023	±0.667	+0.10 ±0.033	3.0	1.35	707	+0.20 ±0.043	4.6
Reticulocytes, %	1947-48	133	0.89 ±0.03	±0.38	120	0.96 ±0.04	±0.49	−0.07 ±0.05	1.4	1.66	...	.....	...
	1948-49	624	0.76 ±0.020	±0.504	433	0.83 ±0.028	±0.586	−0.07 ±0.034	1.8	1.35	336	−0.05 ±0.042	1.2

* The values for 1948-1949 are from the present study; those for 1947-1948 are from Snell, Neel, and Ishibashi.[1]

mean differences between randomly established pairs of similar control and epilated subjects. Once a pair was established, the same pair was retained for all subsequent statistical analyses. A brief history and physical examination were obtained on each subject. A hematologic study employing standard techniques and including red blood cell count, hemoglobin determination, white blood cell count and differential count, volume of packed red cells, red blood cell indices, reticulocyte count, and determination of total plasma proteins, was carried out.

RESULTS AND THEIR INTERPRETATIONS

The results are presented in Table 1 and Table 2. For the purpose of comparison, data from Snell's work have been incorporated in Table 1. Table 2 shows the relationship between the distance from the hypocenter of the atomic bomb explosion and the mean hematologic value.

When Table 1 is examined from a statistical point of view, a significant t value or F test [2] is found in the 1948-1949 study in the red blood cell count, hemoglobin

TABLE 2.—*Relation Between Distance From Hypocenter of Atomic Explosion and Hematologic Findings: Comparison of Mean Values According to Distance*

Observation	Distance from Hypocenter					
	Cases, No.	0-1 Km.	Cases, No.	1-2 Km.	Cases, No.	Over 2 Km.
Red blood cell count, millions	107	4.235 ± 0.04155	524	4.289 ± 0.0175	186	4.356 ± 0.0267
Hemoglobin, gm./100 cc.	107	12.77 ± 0.143	524	12.63 ± 0.050	186	12.61 ± 0.093
Hematocrit reading, %	107	39.27 ± 0.387	524	39.02 ± 0.143	186	38.62 ± 0.234
Mean corpuscular volume	107	93.03 ± 0.730	524	91.27 ± 0.262	186	88.85 ± 0.422
Mean corpuscular hemoglobin	107	30.29 ± 0.243	524	29.53 ± 0.092	186	29.00 ± 0.173
Mean corpuscular hemoglobin concentration	107	32.50 ± 0.148	524	32.36 ± 0.060	186	32.52 ± 0.106
Plasma protein, gm./100 cc.	106	7.37 ± 0.059	522	7.38 ± 0.023	186	7.42 ± 0.041
Leucocyte count	108	9,750 ± 355	530	9,400 ± 128	188	9,721 ± 202
Neutrophiles, %	108	54.55 ± 1.154	525	53.30 ± 0.480	185	53.09 ± 0.902
Lymphocytes, %	108	27.57 ± 0.872	525	28.52 ± 0.355	185	29.77 ± 0.706
Monocytes, %	108	6.94 ± 0.257	525	6.70 ± 0.143	185	6.51 ± 0.214
Eosinophiles, %	108	11.74 ± 0.961	525	11.79 ± 0.410	185	10.33 ± 0.676
Basophiles, %	108	0.75 ± 0.059	525	0.81 ± 0.028	185	0.72 ± 0.052
Reticulocytes, %	68	0.96 ± 0.097	279	0.80 ± 0.031	88	0.77 ± 0.056

determination, hematocrit reading, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total white blood cell count, monocyte count, eosinophile count, basophile count, and reticulocyte count. In addition, in 9 of the 13 comparisons made, the differences between the control group and the exposed group were in the same direction in the 1947-1948 group and the present study. The variability of the findings is greater in the exposed group. It can also be seen from Table 1 that certain changes in the values have been found between the 1947-1948 and 1948-1949 groups. Among the most notable is the fall in the mean red blood cell counts, the hemoglobin values, and the hematocrit readings during the interval between the studies. However, a fall of similar magnitude in these same values is found in the control group.

It should be stated that, in general, hematologic data do not lend themselves well to statistical analysis, particularly when the errors in the hematological methods

2. Values for t in excess of 2.0 indicate differences significant at the probability level of 95%; values in excess of 2.6, differences significant at the 99% probability level. Values for F in excess of 1.16 indicate differences significant at the probability level of 95%; values in excess of 1.24, differences significant at the 99% probability level.

employed are considered. It has been stated that the red blood cell count carried out by trained technicians may show a variation of as much as 16%. Even the most favorable estimates of accuracy permit an error of at least 4% when the count is performed by the same technicians on the same sample of blood.[3] Permissible errors of accuracy of this magnitude make the interpretation of slight statistical variations of hematologic values extremely precarious.

An examination of Table 2 will show that when the values for the exposed group were compared by distance from the hypocenter, 10 of the 14 comparisons show regular progression either from the smallest to the largest mean or from the largest to the smallest mean. This represents twice the number of such patterns that could be expected by chance. However, on closer examination from a clinical hematologic point of view, inconsistencies in the progressions are found. The mean red blood cell count rose as the distance from the hypocenter increased, but the volume of packed red cells fell. The mean corpuscular volume also fell but not in proportion to the changes occurring in the red cell count and hematocrit readings. This would seem to indicate that the changes encountered have no hematologic significance.

The most striking feature of these data as presented is their uniformity. While it is possible that irradiation is responsible for some of the slight changes reported, the comparisons do not reveal significant trends in hematologic values.

SUMMARY AND CONCLUSIONS

This report is a hematologic survey conducted 33 to 44 months after the detonation of the atomic bomb in Hiroshima, Japan. The hematologic findings on a total of 824 survivors are compared with those on a control group of 1,145 residents of Kure. Although statistical differences are apparent in the two groups, when one takes into account errors inherent in the hematologic methods themselves and differences in the possible incidence of parasitism and nutrition it would be unwarranted to attribute the slight changes found to radiation effect.

The data presented here seem to indicate that radiation resulting from the explosion of the atomic bomb in Hiroshima, on Aug. 6, 1945, has not significantly varied the hematologic values as analyzed in this report over a three- to four-year period.

3. Berg, W. N.: Am. Rev. Tuberc. **52**:179, 1945. Berkson, J.; Magath, T. B., and Hurn, M.: Am. J. Physiol. **128**:309, 1940.

PLACENTAL BLOOD SERUM IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Preliminary Report

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INTRODUCTION

DURING the past decade the trend in the therapy of rheumatoid arthritis has been toward the use of hormones. Estrogenic substances, testosterone, pregnenolone, desoxycorticosterone acetate, cortisone, and corticotropin have been used with varying degrees of success and failure. Cortisone and corticotropin are the two most recent additions to the armamentarium. However, they have many significant limitations and contraindications, as reported in the literature by Davison [1] and others. Because of these drawbacks to their universal use, the search for other active hormonal agents continues. Since 1950 I have been using placental blood serum in the therapy of rheumatoid arthritis to evaluate its antirheumatic activity, toxicity, and side-effects.

In 1938, P. S. Hench [2] reviewed the literature for observations of the ameliorating effect of pregnancy on rheumatoid arthritis. He found, from 1864 onward, 10 authors giving accounts of 37 cases of pregnancy among 20 women suffering with active rheumatoid arthritis. These 20 women improved markedly during 34 of their pregnancies. This improvement lasted from several weeks to about nine months post partum. In 1947 Barsi [3] reported on the use of transfusions of whole blood from pregnant women in six cases of rheumatoid arthritis. The six patients were said to have shown marked improvement, but the results have not been confirmed. In 1950, Tufts, Pessin, and Greenwalt [4] reported on the beneficial effects of placental blood serum given in combination with sodium salicylate in nine cases of rheumatoid arthritis. In 1951, Granirer [5] reported on the use of maternal postpartum plasma

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This investigation was supported in part by a grant from the Arthritis and Rheumatism Foundation Fund.

1. Davison, S.: Experiences in the Treatment of Rheumatoid Arthritis with Cortisone, New York J. Med. **51**:2393, 1951.

2. Hench, P. S.: The Ameliorating Effect of Pregnancy on Chronic Atrophic (Infectious Rheumatoid) Arthritis, Fibrositis and Intermittent Hydrarthrosis, Proc. Staff Meet., Mayo Clin. **13**:161, 1938.

3. Barsi, I.: A New Treatment of Rheumatoid Arthritis, Brit. M. J. **2**:252, 1947.

4. Tufts, M.; Pessin, S. B., and Greenwalt, T.: Placental Blood Serum Treatment of Rheumatoid Arthritis, Proc. Staff Meet., St. Mary's Hosp., Milwaukee, Dec. 1950.

5. Granirer, L. W.: Clinical Response of Rheumatoid Arthritis to Postpartum Plasma, J. A. M. A. **146**:995, 1951.

in eight cases. In 1952, Aronson, Levy, Besen, and Leff [6] reported on the satisfactory results obtained with placental blood serum in 33 cases of rheumatoid arthritis and in 2 cases of Marie-Strümpell disease.

PROCEDURES

Method of Obtaining and Preparing Placental Blood Serum.—Immediately after the birth of the baby, the umbilical cord was clamped and cut, and the placental blood was collected under sterile precautions. The proximal clamp on the umbilical cord was released, and the placental blood was permitted to flow freely into sterile collecting tubes of 60 ml. capacity, which were then sealed with rubber stoppers. Stripping of the cord was avoided, since this procedure increased hemolysis. The amount of blood collected in each case varied between 20 and 100 ml. and averaged about 40 ml. The blood was kept in a refrigerator overnight. The supernatant serum was then aseptically transferred and pooled in a 500 ml. vacuum container. The pooled serum was centrifuged at 2,500 R. P. M. for 45 minutes to remove red blood cells and was then transferred into another 500 ml. vacuum container. The placental blood serum was then Seitz-filtered and stored in the refrigerator. This final product was tested for sterility by aerobic and anaerobic culture, and a serological test for syphilis was also done. Some of the specimens were slightly hemolyzed, but this did not prevent their use.

No specimens were taken when the mother was Rh negative or when the mother had a history of syphilis or a positive serological test for syphilis. To avoid the possibility of homologous serum hepatitis, the mothers were carefully screened by history and examination for hepatitis or jaundice from any cause.

Selection of Patients.—All the patients were women with active rheumatoid arthritis. Their ages ranged from 26 to 69 years. The shortest duration of their disease prior to our treatment was 2 years and the longest 31 years, the average being 10 years. Some of these patients suffered from other illnesses, including psoriasis, neurodermatitis, spastic colitis, diabetes mellitus, idiopathic purpura, diverticulosis and secondary anemia. All patients were ambulatory and presented subjective and objective evidence of rheumatoid arthritis in varying degree. All had previously received one or more forms of therapy, such as salicylates, male and female sex hormones, gold, vaccines, cortisone, corticotropin, maternal postpartum plasma, and physical therapy, with little or only temporary improvement.

Because of the possibility of Rh sensitization, it was deemed advisable to restrict the use of placental blood serum to Rh-positive patients only.

Method of Treatment.—Fifteen cases of active rheumatoid arthritis were studied without selection as to severity, stage, duration of disease, or racial origin. They had all been carefully worked up in the clinic, and the patients had received a thorough history and physical examination, a complete blood count, and urine analysis. Blood determinations had been made for erythrocyte sedimentation rate, urea nitrogen, uric acid, and sugar. In addition, each patient was tested for the following blood levels: total protein, albumin, globulin, albumin/globulin ratio, cholesterol and esters, sodium, and potassium. The urinary 17 ketosteroid level was determined in each case and also the Rh type.

6. Aronson, W.; Levy, F.; Besen, L. J., and Leff, M.: Placental Serum Therapy for Rheumatoid Arthritis, Am. J. M. Sc. **223**:144, 1952.

TABLE 1.—*Results of Treatment with Placental Blood Serum in Fifteen Patients*

Case	Patient	Age, Yr.	Duration of Disease, Yr.	Stage of Disease	Classification of Functional Impairment	Treatment		Improvement First Noted	Grade of Response	Reclassification of Functional Impairment	Other Diseases
						Amount	Dates				
1	E. C.	26	2	II	III	470 ml. P. B. S., 32 injections	1/ 4/52-3/ 1/52	2 days	I	I	None
2	C. S.	34	5	III	III	415 ml. P. B. S., 25 injections	1/16/52-2/29/52	2 days	II	II	Secondary anemia
3	M. F.	35	9	II	II	345 ml. P. B. S., 29 injections	12/29/51-2/27/52	7 days	I	I	Psoriasis
4	S. C.	32	13	III	III	655 ml. P. B. S., 57 injections	12/29/51-4/ 3/52	5 days	I	II	Neurodermatitis
5	C. W.	44	4	I	II	515 ml. P. B. S., 35 injections	2/19/52-4/15/52	10 days	III	II	Sinusitis
6	B. B.	37	5	II	III	1,945 ml. P. B. S., 86 injections	2/13/52-7/31/52	7 days	II	II	None
7	H. K.	55	4	II	III	1,180 ml. P. B. S., 79 injections	1/31/52-6/11/52	5 days	III	II	Diverticulitis; spastic colon
8	E. K.	57	7	II	II	290 ml. P. B. S., 26 injections	3/14/52-5/ 2/52	3 days	III	II	None
9	D. S.	59	21	III	III	945 ml. P. B. S., 53 injections	1/ 5/52-4/ 9/52	2 days	III	II	None
10	E. R.	56	15	II	II	340 ml. P. B. S., 22 injections	1/16/52-2/13/52	No effect	IV	II	None
11	E. R.	61	15	II	III	350 ml. P. B. S., 22 injections	1/16/52-2/13/52	No effect	IV	II	None
12	P. L.	75	6	IV	IV	380 ml. P. B. S., 19 injections	5/12/52-6/ 1/52	No effect	IV	IV	Diabetes mellitus
13	L. K.	61	6	III	II	160 ml. P. B. S., 8 injections	7/16/52-8/ 1/52	No effect	IV	II	Idiopathic purpura
14	L. G.	48	4	II	II	325 ml. P. B. S., 17 injections	4/26/52-7/10/52	7 days	II	I	None
15	E. C.	69	31	IV	IV	800 ml. P. B. S., 40 injections	12/17/51-5/ 5/52	No effect	IV	IV	None

Appropriate clinical, hematologic, and roentgenologic examinations; urine analysis, and blood pressure and weight recordings were made at regular intervals. Consultations with the various specialty services were arranged as required. At the end of a course of treatment all the initial laboratory investigations were repeated.

The patients were classified according to the standards of the New York Rheumatism Association.[7] The degree of severity of the disease was graded from Stage I, or early, to Stage IV, or terminal. The functional capacity was graded from Class I, or complete, to Class IV, or completely incapacitated.

The response to therapy was graded from Grade I, or maximum improvement, to Grade IV, no improvement or progression.

Many of the patients were photographed on moving picture film before and after therapy.

Prior to therapy, all the patients were examined by another staff physician, who evaluated their status, paying particular attention to stage of disease, functional capacity, emotional status, and amount and type of sedative or analgesic used. He further evaluated each patient's response to therapy by observations at weekly,

TABLE 2.—*Summary of Results of Treatment with Placental Blood Serum in Fifteen Patients*

	Before Treatment		After Treatment		
			Grade of Response		
Classification	Stage of Disease No. of Patients	Classification of Functional Impairment No. of Patients	No. of Patients	% of Patients	Reclassification of Functional Impairment No. of Patients
I	1	0	3	20	3
II	8	6	3	20	9
III	4	7	4	27	1
IV	2	2	5	33	2

biweekly, or longer intervals. By the use of code systems of recording, the observing and recording physician was prevented from knowing which patient was receiving placental blood serum and which placebo medication.

No special instructions were given as to rest, exercises, vitamins, diets, physical therapy, or the use of analgesics.

Dosage.—In preliminary trials the doses of serum varied from 5 ml. to 250 ml. and were given at intervals of from one to seven days, either intravenously or intramuscularly. An evaluation of the different methods employed revealed that the optimum effect was obtained by giving 30 ml. intravenously daily for the first 14 days, 30 ml. three times a week for the next 2 weeks, then 30 ml. two times a week for 3 weeks, and finally 30 ml. once a week for 1 to 3 weeks. This dosage schedule was frequently altered according to the clinical response obtained.

Controls.—For control or as a placebo, pooled blood serum and pooled blood plasma from nonpregnant women and healthy males were used. This serum or plasma was given at the start, in the middle, or at the end of a course of therapy. The use of the term "new medication" or "new treatment" was avoided as much as possible.

7. Steinbrocker, O.; Traeger, C. H., and Batterman, R. C.: Therapeutic Criteria in Rheumatoid Arthritis, J. A. M. A. **140**:659, 1949.

Untoward Reactions.—At the start of the investigation, an occasional febrile reaction followed the serum administration, which was attributed to pyrogenic contamination. However, with improvement in the method and technique of collection and preparation of the serum, adverse reactions ceased to occur. Over 600 intravenous and intramuscular injections of placental blood serum were given without homologous serum hepatitis as a complication.

RESULTS

The preliminary results obtained with placental blood serum in the treatment of 15 patients with rheumatoid arthritis indicate that this substance exercises a definite antirheumatic effect.

There was definite improvement noted in 67% of the cases. This improvement began as early as the second day in three cases. Nine patients noted improvement within the 1st week, and one began to improve on the 10th day (Table 3). In those patients who responded to treatment there was definite reduction of stiffness and pain on active and passive motion and also of articular and periarticular tenderness. In addition, there were varying degrees of reduction of muscle spasm and

TABLE 3.—*Summary of Response to Treatment with Placental Blood Serum in Fifteen Patients*

Day of Response	No. of Patients
2	3
3	1
5	2
7	3
10	1
No response	5

joint swellings. There were definite improvement in muscle tone and increased joint mobility except for the limitations imposed by fibrous or bony ankylosis. No new process of intra-articular or extra-articular nature developed. There were an increased sense of well-being, more restful sleep, improved appetite, and improved functional capacity and ability to carry on duties. The anxious tense facies disappeared. There was no significant change in weight, blood pressure, blood chemistry, menstrual cycle, or urinary findings. The microcytic hypochromic anemia responded spontaneously to placental blood serum therapy without the use of any other hemic medication. The elevated erythrocyte sedimentation rate fell to normal in two cases. The high leucocyte count shown by some of the patients fell to more normal levels.

A more rapid and effective response was elicited in patients in the premenopausal age group and in those with a history of short duration of the disease.

Of the 15 patients treated (Tables 1 and 2), 3, or 20%, had a Grade I response, complete remission. Three, or 20%, had a Grade II response, major improvement. Four, or 27%, had a Grade III response, minor improvement. The five remaining patients, or 33%, had a Grade IV response, or no response. The patients with no response were in the postmenopausal age group, with ages varying from 56 to 75 years. The duration of their disease varied from 6 to 31 years.

Reclassification of functional impairment showed improvement in eight patients and no change in classification in the seven remaining patients. Two patients whose condition had been refractory to gold salts responded dramatically to placental blood serum. One patient whose condition had been refactory to postpartum plasma and cortisone responded strikingly well to placental blood serum. Two patients who had had toxic side-effects with cortisone responded well to placental blood serum.

Analysis of the results of placebo medication did not reveal any objective evidence of improvement or any long-lasting subjective improvement.

REPORT OF CASES

CASE 1.—E. C., a 26-year-old white woman, appeared in the clinic on Dec. 12, 1951, with a history of rheumatoid arthritis since June, 1949. At first both hands and wrists were involved; then the disease spread to involve her entire upper and lower extremities and back. In September, 1950, she was taking 40 to 60 grains of sodium salicylate a day with little effect. In October, 1950, she became pregnant for the first time. At about the second month of pregnancy, she was given cortisone twice a day intramuscularly for one week and then every other day for one week. There was a weight gain of 15 lb. (6.8 kg.) in two weeks. She felt immediate relief with cortisone therapy, but there was a recurrence of all symptoms soon after cessation of treatment. At about the third month of pregnancy she was again given cortisone injections and then changed to tablets of cortisone, taking 100 mg. orally a day. She felt no relief at all, and since she had gained 48 lb. (21.8 kg.) she discontinued cortisone therapy. At the eighth month of pregnancy she had a spontaneous remission—the swelling persisted, but there was no pain. At two weeks post partum there was a complete exacerbation, and she felt worse than she did prior to her pregnancy, with severe pain, swelling, and limitation of motion.

At the time of her first visit to the clinic, examination revealed many swollen, red, painful joints of the upper and lower extremities. She complained of difficulty in walking up and down stairs, and her activities at home were markedly limited. She was taking 10 to 14 acetylsalicylic acid (A. P. C.) tablets, each with ¼ grain (0.01 gm.) of codeine sulfate, daily for relief. Her condition was classified as Stage II, Functional Class III. Her weight was 120 lb. (54.4 kg.). X-rays revealed osteoporosis and narrowed joint spaces.

Treatment was started on Jan. 4, 1952, 20 ml. of placental blood serum being given intravenously daily. After the second injection, the patient stated that she had stopped taking the tablets and that her fingers felt more limber. After the fifth daily injection, she felt greatly improved; her joint pain, swelling and tenderness had markedly decreased, and she was able to do some things at home. She was given a total of 19 daily injections, then injections three times a week for two weeks, twice a week for three weeks, and finally once a week for one week. During the latter part of her treatment, the dosage was reduced. She received a total of 470 ml. of placental blood serum in 32 injections averaging 15 ml. The last treatment was given on March 1, 1952. She was completely asymptomatic at that time and has remained so for six months. She has resumed all her usual household activities, has returned to work as a typist, and is taking no medication. Her weight is 119 lb. (54 kg.). The response to treatment was Grade I and the reclassification of function was Class I.

The following tabulation lists the significant laboratory findings:

Hemogram:	Before Treatment	After Treatment
Hemoglobin (Haden-Hausser)	74%; 11 gm.	90%; 13.5 gm.
Red blood cells	3,750,000	4,730,000
White blood cells	11,400	6,050
Neutrophiles	60	48
Band cells	0	4
Eosinophiles	1	1
Lymphocytes	36	40
Monocytes	2	6
Basophiles	1	1
Sedimentation rate (Westergren)	47 mm.	15 mm.

Blood levels:		
Sodium	311 mg.	302 mg.
Potassium	17.2 mg.	17.4 mg.
Urea nitrogen	13 mg.	15.1 mg.
Sugar	95 mg.	85 mg.
Total protein	7.0 gm.	7.0 gm.
Albumin	4.3 gm.	3.9 gm.
Globulin	2.7 gm.	3.1 gm.
A/G ratio	1.6	1.3
Uric acid	4.6 mg.	1.7 mg.
Total cholesterol	141 mg.	135 mg.
Free cholesterol	25 mg.	30 mg.
Urinary 17-ketosteroids:	4.6 mg.	4.3 mg.

CASE 2.—C. S., a 34-year-old Negro woman, was first seen on Dec. 5, 1951, with a history of rheumatoid arthritis since 1946. At that time, after the birth of her first child by Caesarean section, lobar pneumonia developed. About one month later she began to have multiple joint pains, swelling, tenderness, and limitation of motion. These symptoms continued and increased in intensity, involving many joints, until the fifth month of her second pregnancy, in 1949. She went into a stage of spontaneous remission which persisted until the third postpartum week, when a complete and severe exacerbation occurred. Her condition gradually worsened until her third pregnancy, in 1950, when she had another remission during the fifth month of gestation. Once again there was an exacerbation in the postpartum period. She had received treatment with vaccines, salicylates, and gold salts, with little or no effect.

Examination at the first clinic visit revealed many swollen, painful, and tender central and peripheral joints with marked limitation of motion and fibrous ankylosis. Her activities were markedly limited. She had difficulty in dressing, eating, and walking; she could not do housework, and she was unable to care for her children. She was taking 10 to 12 tablets of acetylsalicylic acid, of 5 grains (0.32 gm.) each, a day in order to obtain a little relief. Her condition was classified as Stage III, Functional Class III. Her weight was 106 lb. (48.1 kg.). X-rays revealed osteoporosis and some cartilaginous destruction.

Treatment was started on Jan. 9, 1952, 20 ml. of placental blood serum being given intravenously daily for two days. At that time the patient stated that the pain in her fingers had decreased and that all her joints felt much better. Without the patient's knowledge, placebo medication was substituted for the next five days. There was a recurrence of her complaints to the original level of intensity. A course of placental blood serum therapy was instituted on Jan. 16. Once again, after 48 hours, the patient stated that she felt better. Pain, stiffness, and joint swelling had decreased. She was able to move her joints more freely. She reduced her dosage of acetylsalicylic acid to four tablets a day. As treatment continued, her subjective and objective findings decreased, and she felt and looked much better. Fourteen daily injections of 20 ml. of placental blood serum were given intravenously, followed by 10-ml. doses three times a week for three weeks and then twice a week for one week. The patient received a total of 415 ml. of placental blood serum in 25 injections, the average dose being 15 ml. The last treatment was given on Feb. 29. At this time, she was completely asymptomatic except for the permanent joint changes, and she has remained so for six months. She has resumed all her household activities and takes full care of her children. Her weight is 107 lb. (48.5 kg.). The response to treatment was Grade II, and the reclassification of function was Class II.

The following tabulation lists the significant laboratory findings:

Hemogram:	Before Treatment	After Treatment
Hemoglobin (Haden-Hausser)	47%; 7.1 gm.	59%; 9 gm.
Red blood cells	3,080,000	3,650,000
White blood cells	17,600	9,000
Neutrophiles	58	43
Band cells	0	3
Eosinophiles	2	1
Lymphocytes	38	49
Monocytes	2	4
Sedimentation rate (Westergren):	104 mm.	142 mm.

Blood levels:		
Sodium	327 mg.	321 mg.
Potassium	16 mg.	15 mg.
Urea nitrogen	14 mg.	14.3 mg.
Sugar	79 mg.	92 mg.
Total protein	7.2 gm.	9.2 gm.
Albumin	2.8 gm.	2.8 gm.
Globulin	4.4 gm.	6.4 gm.
A/G ratio	0.6	0.5
Uric acid	2.7 mg.	3.1 mg.
Total cholesterol	163 mg.	129 mg.
Free cholesterol	46 mg.	40 mg.
Urinary 17-ketosteroids	5.5 mg.	5.0 mg.

CASE 9.—D. S., a 59-year-old white woman, was first seen in the clinic in 1950 with a history of rheumatoid arthritis since 1930. Originally, symptoms were in the metacarpophalangeal and interphalangeal joints of both hands. The disease spread to involve her wrists, elbows, knees, and ankles. There had been many acute exacerbations.

At the time of initial examination, the patient had the typical "seal flipper" hands, with pain, tenderness, and limitation of motion of the upper and lower extremities, as well as multiple subluxations of the fingers. Her ability to perform her household duties was limited by the pain and deformities. She had received previous therapy with vaccines and salicylates, with very little effect. She was taking approximately 15 acetylsalicylic acid tablets (5 grains) a day. Her condition was classified as Stage III, Functional Class III. Her weight was 132 lb. (59.9 kg.). X-rays revealed osteoporosis with some subchondral bone destruction.

Treatment was started on Jan. 5, 1952, 20 ml. of placental blood serum being given daily. The patient noted improvement in her condition beginning after the second intravenous injection. She received a total of 945 ml. in 53 injections, which were given until April 9. Her course consisted of 40 daily injections, then 3 injections a week for four weeks. There was a moderate improvement in this case. The pain, heat, and tenderness of the joints were greatly relieved; no new rheumatic processes developed. The patient was able to perform more of her household duties. She has maintained her improvement for six months without regression to her previous degree of joint inflammation. Her weight is 134 lb. (60.8 kg.). The response to treatment was Grade III and the reclassification of function was Class II.

The following tabulation lists the significant laboratory findings:

Hemogram:	Before Treatment	After Treatment
Hemoglobin (Haden-Hausser)	70%; 10.5 gm.	80%; 12 gm.
Red blood cells	3,670,000	3,970,000
White blood cells	6,000	5,250
Neutrophiles	77	66
Lymphocytes	20	27
Monocytes	3	2
Band cells	0	4
Eosinophiles	0	1
Sedimentation rate (Westergren)	65 mm.	81 mm.
Blood levels:		
Sodium	333 mg.	325 mg.
Potassium	17.3 mg.	16.2 mg.
Urea nitrogen	18 mg.	15.1 mg.
Sugar	95 mg.	85 mg.
Total protein	7.6 gm.	7.0 gm.
Albumin	4.1 gm.	3.9 gm.
Globulin	3.5 gm.	3.1 gm.
A/G ratio	1.2	1.2
Uric acid	2.9 mg.	1.7 mg.
Total cholesterol	185 mg.	170 mg.
Free cholesterol	55 mg.	58 mg.
Urinary 17-ketosteroids:	2.9 mg.	4.7 mg.

CASE 12.—P. L., a 75-year-old white woman, was first seen in 1950 with a history of rheumatoid arthritis since 1945. All her central and peripheral joints were involved, with pain, swelling, redness, tenderness, and marked limitation of motion. She was confined to her bed or chair, and she could walk only a few steps with the aid of a cane. She had diabetes mellitus, controlled by diet, without the use of any insulin. She had frequent episodes of recurrent joint involvement. She had received previous therapy with vaccines, pregnenolone, and desoxycorticosterone acetate, with no effect.

Immediately prior to the beginning of treatment, the patient was bedridden with severe joint symptoms. She was taking 4 grains of codeine sulfate a day and 30 grains of acetylsalicylic acid a day in order to obtain some relief. Her condition was classified as Stage IV, Functional Class IV. Her weight was 140 lb. (63.5 kg.). X-rays showed cartilaginous and bone destruction with evidence of ankylosis and joint deformity.

Treatment was started on May 12, 1952, and continued to June 1. The patient received a total of 380 ml. of placental blood serum in 19 daily injections averaging 20 ml. There was no response to this treatment. Her weight is 141 lb. (64 kg.). The response to treatment was Grade IV; reclassification of function was Class IV.

The significant laboratory findings are listed in the following tabulation:

Hemogram:	Before Treatment	After Treatment
Hemoglobin (Haden-Hausser)	77%; 11.5 gm.	79%; 11.7 gm.
Red blood cells	4,480,000	5,100,000
White blood cells	10,850	11,900
Neutrophiles	68	56
Band cells	3	4
Eosinophiles	1	3
Lymphocytes	27	35
Monocytes	1	2
Sedimentation rate (Westergren)	60 mm.	58 mm.
Blood levels:		
Sodium	328 mg.	331 mg.
Potassium	15 mg.	16.2 mg.
Urea nitrogen	13 mg.	15 mg.
Sugar	175 mg.	180 mg.
Total protein	6.7 gm.	7.2 gm.
Albumin	4.2 gm.	3.5 gm.
Globulin	2.7 gm.	3.7 gm.
A/G ratio	1.6	0.9
Uric Acid	2.3 mg.	3 mg.
Total cholesterol	157 mg.	161 mg.
Free cholesterol	50 mg.	54 mg.
Urinary 17-ketosteroids	9 mg.	10.5 mg.

COMMENT

The fact that rheumatoid arthritis may change its course spontaneously has been noted by many observers. In order for therapeutic value to be attributed to a new method of treatment, it must give a rapid and long-lasting result. Pregnancy has a definite ameliorating effect on rheumatoid arthritis, but the effect does not extend far beyond the postpartum period. Placental blood serum produced a rapid, marked, and sustained improvement for six months in the systemic and local manifestations of rheumatoid arthritis in 10 of the 15 cases included in this preliminary report. Further observation is required to determine the duration of this improvement.

The active therapeutic principle in placental blood serum is unknown. The results obtained indicate that the active principle is not cortisone or corticotropin, because treatment can be discontinued without maintenance therapy and no toxic side-effects are noted.

Opsahl, Long, and Fry,[8] Jailer and Knowlton,[9] and Opsahl and Long [10] have reported experimental evidence of the elaboration of "adrenal-cortex-like hormones and adrenotropic hormones" by the placenta.

Further experimentation and observation are necessary to determine the qualitative and quantitative distribution of active principles in placental blood serum.

SUMMARY

Fifteen patients with rheumatoid arthritis were treated with placental blood serum. In the 10 who responded to this treatment, the results were rapid and dramatic and were maintained without additional therapy.

The technique of obtaining placental blood serum and its method of preparation are described. The serum may be readily obtained and prepared without great cost. There are no contraindications to its general use at present except Rh negativity. There were no toxic side-effects produced by its use.

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PAROXYSMAL VENTRICULAR TACHYCARDIA TREATED WITH INTRAVENOUS INJECTIONS OF QUINIDINE

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THE INTRAVENOUS administration of quinidine has not been accepted generally because of serious reactions following its use by this route.[1] Although intravenous quinidine preparations are known to be effective in terminating paroxysmal ventricular tachycardia,[2] their use has been delayed because serious side-effects have occurred when they have been given for this purpose.[3] There are few reports describing its use in a significant number of attacks of ventricular tachycardia. Hepburn and Rykert [2g] recorded nine instances, and normal sinus rhythm was restored in eight. Recently Armbrust and Levine,[2a] in analyzing 107 cases of

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paroxysmal ventricular tachycardia, described 31 attacks treated with intravenous quinidine. In 20 of the attacks, conversion to normal sinus rhythm occurred at a time which indicated a response to quinidine therapy. Herrmann and Hejtmancik [2f] found it effective in two of three cases, and Clagett [2b] successfully treated three patients. Strong and Munroe [2e] and, more recently, Bell and his associates [2c] have had satisfactory experience with large doses of quinidine given intravenously when smaller amounts had failed to restore the rhythm to normal.

During the past 12 years quinidine has been used intravenously at the State University of Iowa Hospitals to treat 28 attacks of ventricular tachycardia occurring in 11 patients. Thirty-two injections were given. Quinidine sulfate was used for only one attack, while the remainder were treated with quinidine lactate or quinidine gluconate. The dose varied from 65 mg. to 0.65 gm. The 10 ml. ampules of the lactate and gluconate solutions were used undiluted or diluted to 20 ml. with

Effects of Intravenous Injection of Quinidine in Ventricular Tachycardia

Patient No.	Age, Yr.	Type of Disease *	Attacks, No.	Injections, No.	Result	Toxic Effects
1.....	61	ASHD	1	1	No response	Death (see text)
2 †.....	52	ASHD	7	7	Immediate termination	Nausea, vomiting, one convulsion
.....	..	.....	1	4	Termination 2 hr. after injection	None
3 †.....	47	ASHD	1	2	Initial slowing, conversion to auricular tachycardia in 15 min.	None
.....	..	.....	1	1	No response	None
4.....	37	RHD	1	1	Immediate termination	None
5.....	82	ASHD	1	1	Immediate termination	None
6.....	55	RHD	4	4	Immediate termination	None
7.....	55	ASHD	6	6	Immediate termination	Vomiting once
8.....	70	ASHD	1	1	Immediate termination	None
9.....	68	ASHD	1	1	Immediate termination	None
10.....	73	ASHD	1	1	Immediate termination	Nausea and vomiting
11.....	59	None	2	2	Immediate termination	None

* Explanation of abbreviations: ASHD, arteriosclerotic heart disease; RHD, rheumatic heart disease.
† Previously reported by Chapman.[2d]

isotonic sodium chloride solution. Each injection was given very slowly. Auscultation of the heart was done throughout the period of injection, and, whenever possible, continuous electrocardiograms were recorded during and after the injection. Two of the patients included in this series have been reported previously by Chapman.[2d]

RESULTS

The responses to treatment can be divided into those which occurred immediately and those which were delayed.

Immediate Responses.—Twenty-four attacks were terminated by quinidine, either during the injection or within a few minutes. Dramatic clinical improvement was seen upon termination of the paroxysm in 18 attacks. Three patients, comatose at the time of injection, recovered. Eight patients were described as critically or seriously ill or moribund at the time the injection was begun. In 10 patients there was an abrupt rise in the blood pressure from shock levels to normal. There were no deaths during or immediately after an injection of quinidine, although four patients died subsequently of other causes, including paroxysms of ventricular

tachycardia not treated with quinidine. A summary of all the attacks of ventricular tachycardia in the series is shown in the accompanying Table. Representative examples of the immediate type of response follow.

CASE 4.—A 37-year-old white man had had tachycardia for 9 days prior to admission. He had been observed previously in the outpatient department because of recurring paroxysms of tachycardia but had never presented himself at the time of an attack. He had rheumatic heart disease with mitral stenosis. He was delirious, apprehensive, cyanotic, dyspneic, and dehydrated at the time of admission on Feb. 14, 1947. The cardiac rate was 187 per minute, and the blood pressure was 90/70 mm. Hg. Quinidine lactate was given intravenously at the rate of 65 mg. per minute while a continuous electrocardiogram was recorded. The ventricular tachycardia was terminated abruptly after 0.26 gm. had been given (Fig. 1). Details of his subsequent course are unknown, although he is still living and has had several more attacks of tachycardia.

CASE 5.—An 82-year-old white man was being treated in the urology service for carcinoma of the prostate, which had metastasized widely. While he was on the bedpan, severe precordial pain, dyspnea, and shock developed. The electrocardiogram was interpreted as showing the

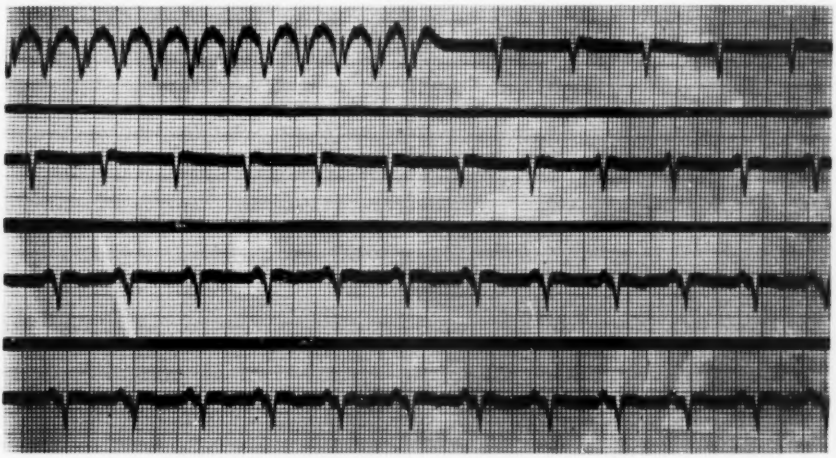

Fig. 1 (Case 4, Lead III).—Ventricular tachycardia at a rate of 187 per minute, with abrupt termination after 0.26 gm. of quinidine lactate had been administered intravenously over a period of four minutes. The pacemaker immediately after the attack is in a lower center, probably the atrioventricular node, after which there occurs a gradual transition to sinus rhythm.

changes of anterior myocardial infarction. The patient's progress was uneventful until the 14th day, when a paroxysm of ventricular tachycardia at a rate of 168 per minute developed. He was given 0.65 gm. of quinidine lactate intravenously at the rate of 65 mg. per minute. Within five minutes after the administration of quinidine, sinus rhythm was restored at a rate of 130 per minute and the patient was definitely improved. He recovered and later was discharged from the hospital. He died 14 months later of carcinomatosis.

CASE 7.[4]—This patient was first seen at the age of 52, when he was admitted to Mercy Hospital 10 hours after the sudden onset of dyspnea and vertigo while mowing his lawn. He had been well previously. He had a ventricular tachycardia at a rate of 200 per minute, and his blood pressure was 85/70 mm. Hg. During the first two days in the hospital, he received, without effect, a total of 0.975 gm. of quinidine intravenously. The preparation was a brown solution of quinidine lactate. On the third day a clear solution of quinidine lactate was obtained, and after 130 mg. had been injected the heart rate abruptly slowed to 120 per minute. Within a few

4. The first two attacks in Case 7 are reported by the courtesy of Dr. J. H. Wolfe, Iowa City.

minutes it was 72 per minute and an electrocardiogram revealed a normal sinus rhythm. The patient immediately improved, and the blood pressure rose to 118/80 mm. Hg. Quinidine by mouth, 0.2 gm. every six hours, was continued, and the patient was discharged three days later.

A second attack occurred, on Oct. 3, 1949. The patient had not taken quinidine orally for two months, and entered Mercy Hospital six hours after the onset of weakness, vertigo, and sweating. Ventricular tachycardia at a rate of 200 per minute was present, and the blood pressure was 80/0 mm. Hg. After unsuccessful attempts to control the rhythm with quinidine by mouth, 0.52 gm. of quinidine lactate was administered intravenously at a rate of 65 mg. per minute. The heart rate slowed abruptly to 80 per minute. Mild nausea occurred, but there was immediate clinical improvement. The patient was discharged two days later on a regimen of 0.2 gm. of quinidine orally every six hours.

The next attack occurred on Jan. 8, 1952, when the patient was admitted to the University Hospitals because of weakness, cyanosis, and tachycardia. The blood pressure was 95/60 mm. Hg, and the cardiac rate was 157 per minute. Quinidine gluconate was administered intra-

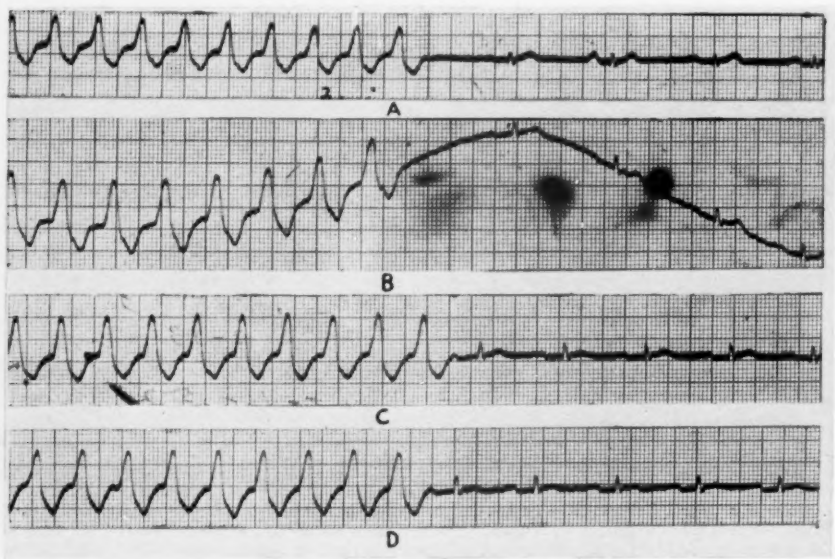

Fig. 2 (Case 7, Lead II).—Four attacks of ventricular tachycardia treated with intravenous administration of quinidine gluconate occurred. *A* (Jan. 8, 1952), rate, 157 per minute; dose, 0.130 gm. in three minutes. *B* (March 29, 1952), rate, 130 per minute; dose, 0.64 gm. in 16 minutes. *C* (May 16, 1952), rate, 150 per minute; dose, 0.36 gm. in five and one-half minutes. *D* (June 19, 1952), rate, 142 per minute; dose, 0.2 gm. in three minutes.

venously, 130 mg. in three minutes. Normal sinus rhythm was reestablished abruptly at a rate of 65 per minute (Fig. 2*A*). The blood pressure rose immediately to 130/90 mm. Hg. The patient was discharged from the hospital on a regimen of 0.2 gm. of quinidine orally every six hours.

Three more attacks have been observed. On March 29, 1952, the ventricular rate was 130 per minute during the paroxysm and 0.65 gm. of quinidine gluconate was administered intravenously over a period of 16 minutes. Normal sinus rhythm was restored abruptly at a rate of 66 per minute (Fig. 2*B*). The prophylactic dose of quinidine was increased from 0.8 gm. to 1.2 gm. per day. The patient returned again, on May 16, 1952, six hours after the onset of another paroxysm. The ventricular rate was 150 per minute, and after he had received 0.36 gm. of quinidine gluconate intravenously normal sinus rhythm was restored at a rate of 79 per minute (Fig. 2*C*). The prophylactic oral dose of quinidine was further increased to 2.2 gm. per day.

Another attack occurred, on June 19, 1952. The ventricular rate was 142 per minute. Quinidine gluconate was administered intravenously, 0.2 gm. in three minutes, and normal sinus rhythm was restored abruptly at a rate of 81 per minute (Fig. 2*D*).

CASE 9.—A 68-year-old white man entered the hospital on Oct. 17, 1949. He had had angina pectoris for two years. The electrocardiogram at the time of admission was characterized by the changes indicative of left ventricular hypertrophy. While he was under observation, severe retrosternal chest pain developed, and he suddenly became very ill, with a ventricular tachycardia at a rate of 125 per minute. Quinidine lactate was given intravenously at the rate of 65 mg. per minute, and after 130 mg. had been administered the cardiac rate fell to 110 per minute. When 0.3 gm. had been given, sinus rhythm was restored and the chest pain improved promptly (Fig. 3). The patient was later discharged, taking quinidine orally. His subsequent course is unknown, except that he died suddenly on April 15, 1951.

CASE 10.—A 73-year-old white man had had exertional dyspnea and angina pectoris for several months and one week before admission had a myocardial infarction, after which he was unconscious for several hours. He was acutely ill upon admission, and the electrocardiogram revealed auricular fibrillation and changes indicative of recent posterior myocardial infarction. On the eleventh hospital day he was found in shock. He had a ventricular tachycardia with a

Fig. 3 (Case 9, Lead II).—Ventricular tachycardia at a rate of 125 per minute. Abrupt restoration of sinus rhythm occurred after 0.3 gm. of quinidine lactate had been administered intravenously in five minutes.

Fig. 4 (Case 10, Lead II).—Ventricular tachycardia at a rate of 176 per minute. Abrupt termination occurred after 0.26 gm. of quinidine gluconate had been administered intravenously in two and one-half minutes. Auricular fibrillation existing prior to the attack of ventricular tachycardia continued afterward.

rate of 176 per minute. He was treated with quinidine gluconate intravenously, receiving 0.26 gm. in two and one-half minutes, after which he became nauseated and vomited. The heart rate slowed abruptly to 62 per minute, and the patient was much improved (Fig. 4). Auricular fibrillation continued. Oral administration of quinidine, 0.2 gm. each four hours, was begun, but four days later a second paroxysm of ventricular tachycardia appeared and the patient died before quinidine could be administered intravenously.

CASE 11.—A 55-year-old white woman entered the University Hospitals, on April 17, 1951, having been unconscious for four hours. She had been working in her garden when she suddenly became weak, began to perspire profusely, and collapsed. There was a history of previous episodes of paroxysmal rapid heart action 25 years before. Upon admission, the patient was cyanotic and comatose and was thought to be moribund. The blood pressure was 40/0 mm. Hg. There was a ventricular tachycardia at a rate of 220 per minute. Quinidine gluconate was injected intravenously at a rate of 65 mg. per minute. When 0.26 gm. had been given, the cardiac rate slowed abruptly to 80 per minute and the blood pressure rose to 85/46 mm. Hg. Improvement was immediate, and an electrocardiogram revealed a normal sinus rhythm. Quinidine by mouth, 0.2 gm. every three hours, was prescribed upon discharge, and the patient had no further difficulty for two months.

A second paroxysm of ventricular tachycardia then occurred, and the patient was readmitted with a ventricular rate of 150 per minute. Quinidine gluconate was injected intravenously, 0.26 gm. in four minutes, at which time there was abrupt restoration of normal sinus rhythm at a rate of 107 per minute (Fig. 5). It was noted by auscultation that for 30 seconds preceding the termination of the paroxysm the heart tones became clearer and the rate slowed slightly. Oral use of quinidine sulfate, 0.2 gm. every three hours, has been continued. The patient reported that on one occasion she failed to take the quinidine and shortly thereafter had a paroxysm of rapid heart action lasting 40 minutes, which terminated after she took 0.4 gm. of quinidine orally. Otherwise, she has continued well. A diagnosis of organic heart disease has not been made.

Delayed Responses.—Six injections of quinidine lactate were given intravenously for two attacks of ventricular tachycardia in two patients (Cases 2 and 3 in the Table), in which only slowing of the rate occurred at the time of injection. One patient (Case 2) received four injections of 0.65 gm. each in less than 24 hours. Slowing of the heart rate occurred after each injection, but normal sinus rhythm was not restored until two hours after the last injection. In the other patient (Case 3) the ventricular tachycardia was replaced by auricular tachycardia 15 minutes after the injection of 0.65 gm.

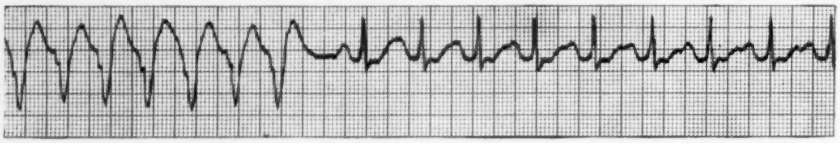

Fig. 5 (Case 11, Lead II).—Ventricular tachycardia at a rate of 150 per minute. There was abrupt restoration of sinus rhythm after 0.26 gm. of quinidine gluconate had been administered intravenously in four minutes.

Failures.—Intravenous administration of quinidine failed to terminate two attacks of ventricular tachycardia. One attack (Case 3 in the Table) continued after 0.65 gm. had been administered, only to terminate spontaneously 10 hours later. The other failure (Case 1 in the Table) occurred in a 61-year-old white man who was admitted two days after having had an acute myocardial infarction. His progress was uneventful until the 28th day, when he had a minor convulsive seizure followed by extreme dyspnea, sweating, and shock. He had a ventricular tachycardia at a rate of 200 per minute, and his condition deteriorated rapidly. By the time a solution of quinidine sulfate was prepared, he was moribund. After 130 mg. had been injected, he died.

COMMENT

The serious nature of sustained or paroyxsmal ventricular tachycardia is recognized.[5] It often presents a sudden emergency, demanding prompt treatment if the patient is to survive. In a few instances, paroxysmal ventricular tachycardia occurs in patients who have no demonstrable heart disease,[2a] but even in this circumstance the patient may be critically ill, as illustrated by Case 11.

5. (*a*) Friedberg, C. K.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1949. (*b*) Levine, S. A.: Clinical Heart Disease, Ed. 3, Philadelphia, W. B. Saunders Company, 1947. Gold.[3c]

When the patient does not require immediate treatment, quinidine by mouth is acceptable.[6] Even so, some will be unable to tolerate it orally. Intramuscular quinidine preparations have been used successfully,[7] but the only material available until recently [7b] has been quinidine hydrochloride, which we have found causes pain or sterile abscesses at the site of injection. The time required for the conversion of the tachycardia and the amounts of quinidine necessary are significantly greater when the drug is administered intramuscularly than when it is administered intravenously.[7d] Intravenous injection of quinidine is indicated in the effort to control promptly ventricular tachycardia in seriously ill patients and in those who cannot tolerate the drug orally.

Certain conditions should be met if quinidine is to be used intravenously. If the lactate or gluconate preparations are to be used, it is recommended that the 10 ml. ampules, containing 0.65 and 0.8 gm. of quinidine, respectively, be diluted to 20 ml. with isotonic sodium chloride solution. A 20-ml. volume of fluid is convenient to use, and the rate of injection is controlled easily. The rate of injection should be timed accurately so that no more than 65 mg. of quinidine is injected per minute. Continuous auscultation of the heart should be carried out in every case, and either a change in the quality of the heart sounds or a change in the cardiac rate is an indication to discontinue the injection. Whenever possible, a continuous recording direct-writing electrocardiograph should be used, so that any change in the configuration of the QRS complex may be detected, in which case the injection should be discontinued. Restoration of normal sinus rhythm or the substitution of some other mechanism will be apparent immediately.

The safety and effectiveness of the method is emphasized in the Table and in the case reports. Critically ill and moribund patients have recovered promptly, although the immediate preinjection prognosis was thought to be grave. However, in Case 1 intravenous injection of quinidine failed to terminate the paroxysm, although the death of this patient cannot be ascribed unequivocally to quinidine in view of his status prior to injection of the drug. Contrary to other reports,[7d] our experience suggests that the quinidine lactate solution has deteriorated when it turns brown and then is ineffective.

The therapeutic action of quinidine is thought to be due to its effect in decreasing myocardial irritability and prolonging the refractory period of cardiac muscle.[8] In ventricular tachycardia quinidine presumably suppresses the ectopic focus selectively and permits the sinus node and conducting system of the heart to function normally. In the instances herein reported, in which the termination of the tachy-

6. Zimmerman, S. L.: Ventricular Tachycardia: A Report of 10 Cases, 8 of Which Were Treated with Quinidine with Recovery in 7, Ann. Int. Med. **23**:634, 1945.

7. (*a*) Riseman, J. E. F., and Linenthal, H.: Paroxysmal Ventricular Tachycardia, Am. Heart J. **22**:219, 1941. (*b*) Bellet, S., and Urbach, J.: A New Intramuscular Preparation of Quinidine (Quinidine Gluconate), J. Lab. & Clin. Med. **34**:1118, 1949. (*c*) Beers, S. D., and de la Chapelle, C. E.: An Unusual Case of Ventricular Tachycardia, Ann. Int. Med. **27**:441, 1947. (*d*) Sturnick, M. I.; Riseman, J. E. F., and Sagall, E. L.: Studies on the Action of Quinidine in Man: II. Intramuscular Administration of a Soluble Preparation of Quinidine in the Treatment of Acute Cardiac Arrhythmias, J. A. M. A. **121**:917, 1943. (*e*) Sagall, Horn, and Riseman.[3a] (*f*) Blinder, and others.[3b]

8. Gold.[3c] Friedberg.[5a]

cardia was recorded electrocardiographically, and in the instance reported by Greenfield and Reiss [9] the ectopic ventricular focus ceased discharging abruptly and a supraventricular mechanism resumed immediately.

Large doses of quinidine produce toxic effects on the myocardium, central nervous system, and gastrointestinal tract. In this series the chief side-effects have been nausea and vomiting. In a few patients profuse sweating developed. One patient had a convulsive seizure after 0.65 gm. had been administered, but he was later given the same amount repeatedly without ill effect. Kalmansohn and Sampson [10] and Sokolow and Edgar [11] have found that toxic symptoms are directly related to the blood level of quinidine. Blinder and associates [3b] reported seven intravenous injections of 0.65 gm. of quinidine lactate at rates in excess of 130 mg. per minute, and all patients exhibited toxic effects. Thus the rate of injection becomes of extreme importance. We have not observed significant toxic effects during or following injection when the rate was not in excess of 65 mg. per minute. Nevertheless, precipitation of cardiac standstill or ventricular fibrillation remains a possibility, but we believe this very unlikely if the principles of slow injection, simultaneous auscultation of the heart, and the recording of a direct-writing electrocardiograph are followed.

In our cases large doses of quinidine have not been required, but Pordy and associates,[12] Strong and Munroe,[2e] and Bell and associates [2c] have had good results with large intravenous doses of quinidine when smaller amounts were unsuccessful.

SUMMARY

Eleven patients with paroxysmal ventricular tachycardia received 32 intravenous injections of quinidine for 28 attacks. Twenty-four attacks were terminated abruptly during or a few minutes after the injection. In two attacks normal sinus rhythm was not restored for several hours. In two instances there was failure to terminate attacks. One patient died during the injection, but death was not necessarily from quinidine toxicity. It is concluded that under the conditions outlined the intravenous use of quinidine is a safe and highly effective means for terminating paroxysms of ventricular tachycardia. It is indicated for the prompt control of ventricular tachycardia in patients who are seriously ill and in patients who cannot tolerate the drug orally.

9. Greenfield, I., and Reiss, J.: Paroxysmal Ventricular Tachycardia: Experience with Quinidine Hydrochloride, Am. Heart J. **42**:631, 1951.

10. Kalmansohn, R. W., and Sampson, J. J.: Studies of Plasma Quinidine Content: II. The Relation to Toxic Manifestations and Therapeutic Effect, Circulation **1**:569, 1950.

11. Sokolow, M., and Edgar, A. L.: Blood Quinidine Concentrations as a Guide in the Treatment of Cardiac Arrhythmias, Circulation **1**:576, 1950.

12. Pordy, L.; Kolker, J., and Levy, H.: Paroxysmal Ventricular Tachycardia of Prolonged Duration, Am. J. Med. **10**:254, 1951.

MECHANISM OF FLUTTER AND FIBRILLATION

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THE PHENOMENON of cardiac fibrillation has been known for more than a century. Its discovery immediately aroused considerable interest, but for several decades before 1946 little attention was paid to the mechanism of this arrhythmia. There were several reasons for this. The circus movement, or reentry mechanism, was accepted by many as a proved fact in flutter and fibrillation. In many books and articles it was stated categorically that flutter and fibrillation are due to a circus-movement, and objections against the theory were not even mentioned. Another obstacle to the study of their mechanism was the difficulty in obtaining flutter and fibrillation in the experimental animal in a practical manner. Ventricular fibrillation can be easily elicited by electrical stimulation. However, it is fatal within a few minutes in those larger mammals which are suitable for research. The cost was excessive in comparison to the briefness of the time available for experimental study. Nor was there a method to induce and to study ventricular flutter experimentally.

In the case of the auricles, flutter and fibrillation can be induced by electrical stimulation but not with any regularity; when they do appear, their duration is unpredictable and all too often too brief for satisfactory experimental study. Combining physostigmine, muscarine, and acetylcholine with electrical stimulation produces longer-lasting arrhythmias but these substances change the condition of the myocardium.

VARIOUS THEORIES OF THE MECHANISM OF FLUTTER AND FIBRILLATION

The recent revival of research in this field was stimulated by the discovery of better methods for inducing flutter and fibrillation in the heart, especially by the topical application of aconitine.[1] Another recent method for inducing auricular flutter is the combination of crushing and electrical stimulation of the auricular muscle.[2]

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This investigation was supported (in part) by a research grant from the National Heart Institute, United States Public Health Service.

1. (*a*) Scherf, D.: Studies on Auricular Tachycardia Caused by Aconitine Administration, Proc. Soc. Exper. Biol. & Med. **64**:233 (Feb.) 1947. (*b*) Scherf, D.; Romano, F. J., and Terranova, R.: Experimental Studies on Auricular Flutter and Auricular Fibrillation, Am. Heart J. **36**:241 (Aug.) 1948.

2. Rosenblueth, A., and Garcia Ramos, J.: Estudios sobre el flutter y la fibrilación: II. La influencia de los obstáculos artificiales en el flutter auricular experimental, Arch. Inst. cardiol. Mexico **17**:1 (Feb.) 1947; Studies on Flutter and Fibrillation: II. Influence of Artificial Obstacles on Experimental Auricular Flutter, Am. Heart J. **33**:677 (May) 1947.

This report reviews briefly the theories of the mechanism of auricular flutter and fibrillation. It discusses experiments which demonstrate that the circus-movement theories are inadequate and that the ectopic-focus theory (theory of tachysystole) is better.

Space does not permit a discussion of all the explanations dealing with the mechanism of these arrhythmias published in the last 100 years. This has been done in several excellent reviews.[3] Most theories were based on experimental data; this is also true for one of the oldest, which postulates the existence of a center in the ventricles coordinating ventricular contractions. Damage to this center would lead to the dissociated fragmentary contractions which appear to exist in fibrillation.

The two theories most compatible with the known facts are the ectopic-focus theory [4] and the circus-movement theory. According to the former, flutter and fibrillation are due to rapid stimulus formation or impulse firing in one or more foci. As early as 1900, fibrillation was called the highest degree of abnormal ectopic stimulus formation, extrasystole being the simplest form.[5] There are many variants of this theory. They concern the number and location of the ectopic foci. According to some, one focus exists in fibrillation; others assume several foci. Some believe that these are located in the sinus node; others, that they are in the auriculoventricular node or in the specific fibers of the ventricles in the case of the ventricular form of the arrhythmia.

The circus-movement, or reentry, theory also has many variants. Garrey, experimenting chiefly on the ventricles, postulated the existence of one or more circus waves within the common muscle.[3a] Lewis and his group, who worked on the dog auricle, believed that a single circus wave circulates up and down the sinus node and around the orifices of the venae cavae.[6] The latter theory has been the most popular. It was even extended, without much justification, to the explanation of auricular tachycardias. Even Rothberger, who was rather critical of Lewis' experiments and interpretations, considered the possibility of numerous circus movements in small areas as the mechanism of ventricular fibrillation.[7]

In our opinion, the ectopic-focus theory is more consistent with the known facts than is the circus-movement theory. The experimental data supporting the ectopic-focus theory have been confirmed repeatedly. On the other hand, the experimental basis for the circus-movement theory has not been adequately confirmed.

The original work of Lewis and his school has been criticized from the beginning. Lewis based his circus-movement theory on two series of experiments. First, he claimed to have determined the path of the circus wave, by means of direct leads, to be around the venae cavae and up or down the sinus node in auricular flutter

3. (*a*) Garrey, W. E.: Auricular Fibrillation, Physiol. Rev. **4**:215 (Apr.) 1924. (*b*) Winterberg, H.: Herzflimmern und Herzflattern, Handb. norm. u. path. Physiol. **7**:663 (Pt. 1) 1926.

4. We use the term "ectopic focus" although it is possible that stimulus formation takes place in the sinus node; it need, therefore, not be ectopic.

5. Hering, H. E.: Zur experimentellen Analyse der Unregelmässigkeiten des Herzschlages, Arch. ges. Physiol. **82**:1 (Sept.) 1900.

6. Lewis, T.: The Mechanism and Graphic Registrations of the Heart Beat, Ed. 3, London, Shaw & Sons, Ltd., 1925.

7. Rothberger, C. J.: Normale und pathologische Physiologie der Rhythmik und Koordination des Herzens, Ergebn. Physiol. **32**:472, 1931.

and fibrillation. In this he succeeded only in one experiment and then only incompletely.[8] The existence of a closed muscular path around the orifices of the great veins has never been demonstrated anatomically.[7] One would have to assume that it is situated posteriorly, near the pulmonary veins, in the left auricle. The second support of the circus-movement theory was the demonstration by Lewis that the vector as calculated from the flutter waves rotated around a circle of 360 degrees. Several objections apply to this. The activity of a small ring of muscle around the venae cavae cannot be responsible for the flutter waves recorded from the chest wall. The F waves, as recorded in the chest leads used by Lewis, are caused by the activity of the entire auricles.[8] A second objection is based on the fact that the flutter waves in the electrocardiogram contain both activation and recovery components, corresponding to the P and the Ta waves.[9] Tachycardia, by shortening of the monophasic action current, causes the Ta waves to shorten; the Ta waves must therefore deepen in order to maintain an area equal and opposite to the P wave.[10] Accordingly, the form of the Ta wave approaches that of an inverted P wave. Obviously, the vectors defined by these waves will have an activation half and an opposite recovery half. Together the parts describe a circle of 360 degrees around the isoelectric center. This is a result of the tachycardia and not an expression of a circus movement.

Inherent in all circus-movement theories is the assumption that a gap of recovered, unexcited tissue exists in front of the head of the circus wave. Accordingly, any strong electrical shock which would depolarize the whole heart should also depolarize this gap and should end the fibrillation. Actually one can abolish auricular and ventricular fibrillation with strong electrical shocks. However, this happens only when these shocks are "properly timed,"[3a] that is, after several successive shocks are administered. A single shock rarely has this effect, as one would expect according to the circus-movement theory.

As stated above, according to Lewis, the central circulating (mother) wave employs a path up or down the sinus node. A broad ligature applied across the sinus node and the adjacent tissues would interrupt the circulating wave and bring flutter to a stop. Or, it is conceivable that the wave takes another path; in such a case the rate and shape of the P waves should change. This was tested experimentally in 17 dogs with postfaradic flutter. In 16 of the animals no such change appeared in the electrocardiogram after the ligature was applied across the sinus node.[11] In only one instance did the flutter stop upon application of the ligature. This, however, often happens in postfaradic flutter merely from handling the auricles. Modifications of these experiments were repeated with identical results.[12]

8. Rothberger, C. J.: Neue Theorien über Flimmern und Flattern, Klin. Wchnschr. **1**:82, 1922, **2**:1407 (July 23) 1923.

9. Prinzmetal, M.; Corday, E.; Brill, I. C.; Sellers, A. L.; Oblath, R. W.; Flieg, W. A., and Kruger, H. E.: Mechanism of Auricular Arrhythmias, Circulation **1**:241 (Feb.) 1950.

10. Scherf, D., and Schaffer, A. I.: The Electrocardiographic Exercise Test, Am. Heart J. **43**:927 (June) 1952.

11. Scherf, D.: Versuche zur Theorie des Vorhofflatterns und Vorhofflimmerns, Ztschr. ges. exper. Med. **61**:30 (May) 1928.

12. Brams, W. A., and Katz, L. N.: The Nature of Experimental Flutter and Fibrillation of the Heart, Am. Heart J. **7**:249 (Dec.) 1931.

It was furthermore found that the form of the flutter waves in postfaradization flutter was in most experiments similar to the P waves of the basic rhythm. Thus, if unusually high P waves existed during sinus rhythm, then unusually high P or F waves appeared during flutter. When these P waves became negative following ligature of certain intra-auricular pathways or ligation of the arteries supplying the sinus node, the flutter waves likewise became negative, with a similar shape. If the P wave was induced to be widened and slurred, the flutter waves did likewise. This was not invariable, but it happened in so many instances that it seemed permissible to conclude that ectopic stimuli during flutter often originate in the same focus as the stimuli of the existing basic rhythm (Fig. 1).

If one auricle is made to contract independently of the other by application of a ligature, then each auricle may exhibit flutter alone after faradization.[13] Obviously, the pathway up or down the sinus node is not indispensable for this arrhythmia.

A case of auricular flutter in man has been reported in which the auricular rate suddenly doubled.[14] A comparison of the explanations offered by the two theories emphasizes the advantages of the ectopic-focus theory. The circus-movement theory has to make the improbable assumption that at the time of the doubling of the rate the length of the path taken by the circus movement was suddenly and exactly halved. On the other hand, the ectopic-focus theory can invoke an established principle to explain the sudden doubling of the rate. At first the auricles responded only to every second stimulus fired by the center (2:1 rhythm); then, without the

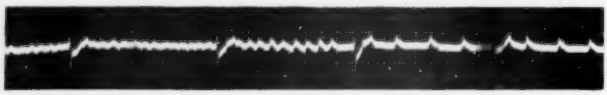

Fig. 1.—Auricular fibrillation followed by flutter and eventually by sinus rhythm after topical application of acetylcholine to the dog auricle. Auriculoventricular conduction is markedly inhibited. Note that the P waves during sinus rhythm closely resemble the flutter waves (Lead II).

latter changing its rate, the auricles began to respond to every stimulus (1:1 rhythm). Sudden doubling of the rate of an auricular tachycardia has been reported.[15] Obviously, the ectopic-focus theory can explain this also; one cannot apply the circus-movement theory to the usual auricular tachycardia because the rate is too slow to permit a continuous circus movement in the available auricular muscle.[6]

Experiments on the tortoise heart, with use of numerous direct leads, indicated that a circus movement is not the usual mechanism of auricular fibrillation.[16] Those who accept the circus-movement theory explain the disappearance of flutter and fibrillation after quinidine and other drugs by the prolongation of the refractory

13. Scherf, D., and Siedek, H.: Über Block zwischen beiden Vorhöfen, Ztschr. klin. Med. **127**:77 (May) 1934.

14. Cookson, H., and Clark-Kennedy, A. E.: Auricular Flutter Presenting a Curious Change in the Auricular Electrocardiogram, Heart **16**:103 (July) 1932.

15. Camp, P. D., and Scherf, D.: Frequenzverdoppelung bei paroxysmalen Tachykardien und Vorhofsflattern, Wien. Arch. inn. Med. **25**:67 (June) 1934.

16. Rijlant, P.: Contraction normale et fibrillations auriculaires et ventriculaires chez la tortue: Les fibrillations des oreillettes et du ventricule intacts, Cardiologia **10**:193, 1946.

phase. Pharmacological investigations revealed, however, that fibrillation disappears also after administration of drugs which do not alter the duration of the refractory phase.[17]

NEW INVESTIGATIONS

The discovery that it is possible to elicit prolonged auricular flutter and fibrillation regularly by the topical application of aconitine [1] enabled us to reinvestigate the mechanism of these arrhythmias. Flutter and fibrillation following administration of aconitine persist for more than one hour without any change in the rate or in the electrocardiographic picture. The experimental results discussed in the following paragraphs clearly indicate that the circus-movement theory cannot apply to these arrhythmias.

1. Application of aconitine on the tip of the appendix of the right or left auricle leads to the appearance of flutter. If the area on which the aconitine had been applied is clamped off from the rest of the auricle, the flutter in the body of the auricle stops immediately and sinus rhythm reappears. The flutter continues, however, in the isolated tip. With removal of the clamp, flutter of both auricles returns immediately.[18] This result proves that the stimuli originate in the tip of the auricular appendix, that is, in the area on which the aconitine has been applied. The interpretation that one is dealing with a local circus movement does not seem permissible, since aconitine causes flutter within a few seconds wherever it is applied in the auricle. It is difficult to assume that every application of aconitine to any part of the auricles would create the complicated conditions making possible a circus movement in a small area. A circular path must be present; it must have a minimum length, which is determined by the velocity of the activation wave and the duration of the refractory phase. Furthermore, such a local circus movement is a mere assumption, the existence of which has never been proved. Garrey was unable to cause fibrillation in small pieces of muscle.[3a] Finally, because the circus path would be minute, the rate of the flutter should be much higher than it actually is.

It is of interest that Garrey noticed many years ago sustained flutter following faradization. It originated from impulses about the site of the electrodes after the faradic current was discontinued. When this area was clamped off, the flutter stopped in the body of the auricle but continued in the clamped-off area.[3a]

2. Cooling the area on which aconitine has been applied stops the existing flutter or fibrillation. Often these arrhythmias disappear immediately on application of the cooling thermode. Removal of the thermode is followed by a quick reappearance of the arrhythmias. This is a consistent, reproducible finding in such experiments. Rare exceptions, which are explainable, will be discussed later. With cautious cooling it is possible to transform fibrillation progressively through flutter and extrasystoles into sinus rhythm.[19] When cooling is discontinued, flutter frequently

17. Van Dongen, K.: The Action of Some Drugs on Fibrillation of the Heart, Arch. internat. pharmacodyn. **53**:80 (April) 1936.

18. Scherf, D.: Experiments on the Origin of Auricular Flutter and Fibrillation, Arch. brasil. cardiol. **1**:147 (June) 1948.

19. (*a*) Scherf, D., and Terranova, R.: Mechanism of Auricular Flutter and Fibrillation, Am. J. Physiol. **159**:137 (Oct.) 1949. (*b*) Scherf.[1b]

reappears at first and the rate quickly accelerates until fibrillation sets in; at other times fibrillation appears immediately, without any appreciable intermediate flutter stage (Fig. 2).

These results also speak in favor of stimulus formation in a center and against the existence of a circulating wave. A circus wave which stops its perpetual motion, for even a fraction of a second, must come to an end. The reappearance of flutter and fibrillation respectively after discontinuation of cooling points to the persistence of an active firing center.

3. The ectopic rhythm which appears after the topical application of aconitine occasionally exhibits a slow rate, of less than 150 beats per minute. The rate gradually increases to about 300 per minute, at which time the tracing has all the earmarks of flutter. The form of the P wave remains, the same in both the slow and the rapid phases [19a]; this shows that the path of activation of the auricles is the same in both phases. Because the two phases merge gradually into each other, because the P wave maintains a constant form in both phases, and because a circus movement is inconceivable with the slow rates, a circus movement cannot be invoked to explain the flutter phase.

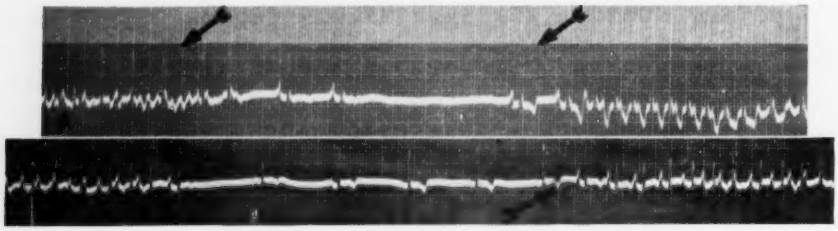

Fig. 2.—*A*, tracing from dog heart, with auricular fibrillation induced by aconitine, applied topically. Cooling the area of application (arrow) stops the fibrillation and restores sinus rhythm. Discontinuation of cooling (arrow) leads to reappearance of flutter, at first with full conduction to the ventricles, and then with 2:1 block; a few seconds later fibrillation reappears. *B*, auricular flutter is present, induced by application of aconitine to the sinus node. Cooling stops the flutter, which originally had a rate of 320. Before the flutter disappears, a considerable slowing of the auricular rate is seen. Discontinuation of the cooling leads again to flutter. (Both tracings were obtained in Lead II). Beginning and end of cooling are marked by arrows.

4. During vagal stimulation in some experiments long pauses appeared between the flutter waves.[19a] These pauses could not occur during a circus movement, because if the circus movement is interrupted it must end.

5. Stretch and pressure applied to the area on which aconitine has been administered increases the existing flutter rate; if the rate exceeds 600 per minute, fibrillation appears.[20] Even after the aconitine flutter or fibrillation has subsided spontaneously, pressure or stretch temporarily elicits it again (Fig. 3).

It is inconceivable how pressure applied by a probe to the small area on which aconitine has been applied would cause the appearance of flutter or would change flutter into fibrillation by altering the speed of a circus movement. The results can be easily explained if one assumes that the flutter and fibrillation result from rapid

20. Scherf, D.; Scharf, M. M., and Goklen, M. F.: Effect of Stretch and Pressure on Stimulus Formation in the Dog's Auricle, Proc. Soc. Exper. Biol. & Med. **70**:708 (April) 1949.

stimulus formation in a center. Both stretch and pressure lead to a lowering of the resting membrane polarization. This reduces the threshold of excitability and may even cause actual firing of stimuli in both nerve and muscle.[21] Stretch is the physiological stimulus for cardiac automaticity in some lower animals. It is probably the basis for the increased sinus rate in patients with auricular distention, a phenomenon usually explained by the Bainbridge reflex.

6. Acetylcholine applied to the area of the head of the sinus node leads to flutter with positive F waves in Lead II. Injection of acetylcholine into the auriculoventricular node region also causes flutter, but the F waves are then deeply inverted.[22] Obviously, in the first instance the auricles are being activated from the region of the head of the sinus node, in the second instance from the auriculoventricular node. Thus, in Figure 4, at the beginning auricular flutter exists, which was induced by the injection of acetylcholine into the interauricular septum at the area in front of the orifice of the coronary sinus vein. Flutter with deeply inverted F waves and a rate of 545 is seen. Cooling of the area of injection was performed

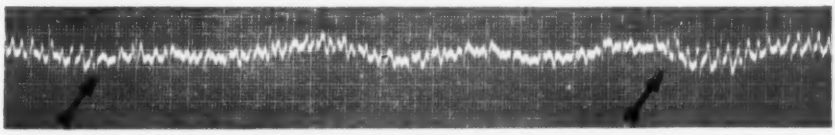

Fig. 3.—Tracing from a dog heart with auricular flutter induced by topical application of aconitine. When the treated area is pressed with a probe (arrow), fibrillation appears. When the probe is removed, flutter reappears (arrow). (Lead II).

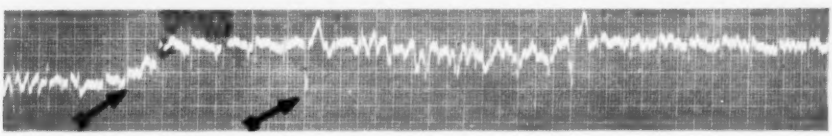

Fig. 4.—Tracing of a dog heart with auricular flutter induced by the injection of acetylcholine into the interauricular septum, near the orifice of the coronary sinus vein (coronary sinus node). Flutter with deeply inverted F waves is seen. At the time indicated by the arrow the injected region was cooled by lifting the heart from its bed and applying the cooling thermode to the coronary sinus vein. The flutter is stopped. An auriculoventricular rhythm appears with deeply inverted P waves (auriculoventricular rhythm) (Lead II). Interruption of the cooling leads to appearance of fibrillation.

by lifting the heart from its bed and by applying the cooling thermode to the coronary sinus vein [23]; this abolishes the flutter, and an auriculoventricular rhythm appears with deeply inverted P waves, presumably originating in the center activated by the acetylcholine. Cessation of the cooling was followed by the reappearance of flutter with deeply inverted F waves; this was quickly followed by fibrillation.

21. Adrian, E. D., and Gelfan, S.: Rhythmic Activity in Skeletal Muscle Fibers, J. Physiol. **78**:271 (June) 1933.

22. Scherf, D., and Chick, F. B.: Abnormal Cardiac Rhythms Caused by Acetylcholine, Circulation **3**:764 (May) 1951.

23. Scherf, D.: Upper Auriculo-Ventricular Rhythm (Coronary Sinus Rhythm) Experimentally Produced, Proc. Soc. Exper. Biol. & Med. **56**:220 (June) 1944.

7. Flutter and fibrillation were immediately arrested by the application of potassium chloride or quinidine to the aconitinized site, whose area was 2 to 4 mm. in diameter.[19a] If a circus wave were moving up or down the sinus node, remote from the aconitinized region, as Lewis postulated, this result would be impossible.

The experiments described in the preceding paragraphs demonstrate that a circus mechanism is inconceivable under the given conditions. This applies not only to a gross circus motion around the venae cavae and through the sinus node but also to one limited to the small area treated by aconitine or faradization.

EFFECT OF VAGAL STIMULATION ON AURICULAR FLUTTER AND FIBRILLATION

To facilitate the treatment of this complex subject, the observed effects of vagal stimulation are explained by its action on the individual myocardial fiber. It is adequately established that vagal stimulation causes a marked shortening of the monophasic action current. Paralleling this is a marked decrease in the absolute and total refractory period. However, under certain conditions just the opposite effects have been noted. It was found that weak vagal stimulation caused a prolongation of the refractory period. Furthermore, after the recovery from strong vagal stimulation there appeared a phase when the refractory period became tem-

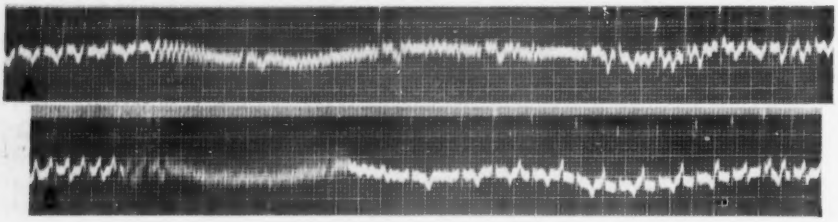

Fig. 5.—*A*, aconitine-induced flutter of the auricles in a dog, with a rate of 300; during vagal stimulation the rate increases to 1,200 per minute and then auricular fibrillation develops. About three seconds after the end of the vagal stimulation the same flutter was observed as at the beginning of the tracing (Lead II). *B*, tracing shows auricular flutter in a dog heart, following application of aconitine to the region of the sinus node. Faradic stimulation of the right vagus nerve in the neck leads to the appearance of fibrillation; the stimulation is discontinued, and sinus rhythm appears. After six sinus beats the flutter recurs (Lead II). Repetition of vagal stimulation causes sinus rhythm again.

porarily prolonged (rebound effect).[24] There is evidence that conduction within the auricle is under certain conditions accelerated by vagal stimulation.[25]

Vagal stimulation usually increases the rates of all types of experimental flutter and fibrillation.[26] In the case of flutter the rate may become accelerated to the point at which fibrillation ensues.

24. Hoffman, B. F.; Siebens, A. A., and Brooks, C. M.: Effect of Vagal Stimulation on Cardiac Excitability, Am. J. Physiol. **169**:377 (May) 1952.

25. Lewis, T., and Drury, A. N.: The Effect of Vagal Stimulation on Intra-Auricular Block Produced by Pressure or Cooling, Heart **10**:179 (April) 1923.

26. (*a*) Winterberg, H.: Über die Wirkung des Nervus vagus und accelerans auf das Flimmern des Herzens, Arch. ges. Physiol. **117**:223 (March) 1907. (*b*) Lewis, T.; Drury, A. N., and Bulger, H. A.: Flutter and Fibrillation Effects of Vagal Stimulation, Heart **8**:141 (May) 1921. (*c*) Scherf, D.; Blumenfeld, S.; Mueller, P., and Beinfield, W. R.: On the Response of Ectopic Tachycardias to Vagus Stimulation, Am. Heart J. **45**:95 (Jan.) 1953. (*d*) Scherf.[1b] (*e*) Rosenblueth.[2]

Figure 5*A* illustrates how vagal stimulation accelerates aconitine-induced flutter from a rate of 300 to 1,200 per minute, whereupon fibrillation ensues. Although the rhythm when the rate is 1,200 has elements of fibrillation in it, yet the auricles can respond to this rate in an almost organized fashion because of the marked reduction of the refractory phase. In the case of fibrillation the rate of the coarser F waves may increase to a most remarkable degree; they can attain rates of 3,500 a minute.

Vagal stimulation facilitates the induction of all types of experimental flutter and fibrillation. Long after the overt effects of a topical application of acetylcholine have disappeared, the auricles and ventricles of the dog heart can be made to fibrillate by any mild stimulus, such as mechanical or electrical shock or cooling. On the other hand, after atropinization it becomes impossible to induce fibrillation by the topical application of aconitine.

Occasionally vagal stimulation does not facilitate or accelerate these experimental arrhythmias. It may either leave the rate unaffected or it may stop a flutter completely. Lewis noted that the stimulation of the vagus with a weak current could arrest flutter that was induced by faradization.[26b] We found that at the end of stimulation of the vagus with a strong current flutter induced by the local application of aconitine was occasionally interrupted[26c] (Fig. 5*B*). These anomalous results can be correlated with the increase of the refractory period which is caused by weak vagal stimulation or which develops as a rebound following strong vagal stimulation.[24]

Another difference between Lewis' results and our is that the arrest of the flutter by vagal stimulation was permanent in his experiments while in ours the flutter recurred quickly. This is due to the difference in the method of induction of the flutter. Lewis induced flutter by faradization. Once the flutter stops for any reason, it will not reappear unless faradization is repeated. On the other hand, we induced flutter by the topical application of aconitine. The latter remains in situ and continues to exert its flutter-inducing effect for a comparatively long time. Interruption of the flutter is followed by a recurrence if the inhibiting factors are discontinued. The cessation of vagal stimulation or the spontaneous disappearance of the rebound effect will therefore be followed by a recurrence of the flutter.

The inefficacy of vagal stimulation on clinical auricular flutter and fibrillation is unexpected in view of the above-mentioned experimental findings. On rare occasions flutter has been accelerated or transformed into fibrillation by carotid sinus compression,[27] or even induced by it.[28] Also, cases have been reported in which flutter and fibrillation have been induced by deep breathing.[29] This is most

27. Rihl, J.: Hochgradige Vorhoftachysystolien mit Überleitungsstörungen und electiver Vaguswirkung, Ztschr. exper. Path. u. Ther. **9**:277 (Aug.) 1911. Wilson, F. N.: Report of a Case of Auricular Flutter in Which Vagus Stimulation Was Followed by an Increase in the Rate of the Circus Rhythm, Heart **11**:61 (Jan.) 1924. Bellet, S.: Diagnosis and Treatment of Cardiac Arrhythmias, M. Clin. North America **30**:1307 (Nov.) 1946.

28. Aalsmeer, W. C.: On the Results and Clinical Significance of Artificial Pricking of the Vagus in Man, Nederl. Maandschr. geneesk. **9**:143 and 305, 1920.

29. Smith, F. M., and Moody, W. B.: The Induction of Premature Contractions and Auricular Fibrillation by Forced Breathing, A. M. A. Arch. Int. Med. **32**:192 (Aug.) 1923. Burak, M., and Scherf, D.: Angina pectoris und paroxysmale Tachykardie, Wien. Arch. inn. Med. **23**:475 (March) 1933.

probably a vagal effect, though variation of auricular distention must also be considered. All these observations are decidedly exceptions. Almost always there is no appreciable effect of vagal stimulation on clinical examples of these arrhythmias, and atropine in permissible doses has rarely any significant action in clinical cases.

The various effects of vagal stimulation in both the experimental and the clinical type of these arrhythmias do not help in evaluating the merits of the circus versus the ectopic focus theories. It is interesting to see how the observed facts can be fitted into either one.

Lewis offered two possible explanations for the increased rate following vagal stimulation. According to one, shortening of the refractory period enables the circus wave to move in a shorter pathway. This, however, seems improbable, since the path around the cardiac veins is already the shortest possible. Moreover, the form of the P waves would change if a different path were employed, for portions of the auricle would be activated in a different sequence. Actually, the form of the flutter waves remains the same during vagal stimulation in spite of even an extreme increase in rate. The second, and more reasonable, explanation offered by Lewis was that the shortening of the refractory phase eliminates islands of refractory tissue in the path of the circulating wave, which can then circulate faster.

The ectopic-focus theory can utilize the shortening of the refractory period just as well, if not better, to explain the vagal effects. If one assumes the presence of a constant stimulus in an area treated with aconitine, then the heart rate is a function of the duration of the refractory period. If one is inclined to assume that stimuli are formed periodically (which is more probable), then the decrease in the duration of the monophasic action current must lead to a faster formation of stimuli.

The marked increase in the rate of flutter and fibrillation due to vagal stimulation so impressed Lewis that he gave it a name, rapid reexcitation.[30] He noted rates as high as 3,500 per minute. Hoffman and his associates recently demonstrated that the refractory period of the individual myocardial fiber can be decreased to 10 milliseconds.[24] This would permit a rate of 100 per second, or 6,000 per minute. Lewis, in order to explain the marked acceleration, postulated that the central wave pursued a path with a markedly shortened diameter. Since aconitine flutter has been definitely shown to originate in a very small area, this explanation cannot apply.

Although the correlation between the observed experimental effects of vagus stimulation and its effect on the individual myocardial fiber appears to be good, it must be noted that there are many gaps. Much more will have to be discovered before one can be satisfied with the correlation between the clinical and the experimental observations.

EFFECT OF STIMULATION OF THE SYMPATHETIC NERVES IN AURICULAR FLUTTER

It is of interest that Lewis, in his otherwise exhaustive studies on auricular flutter, did not report on the effect of sympathetic stimulation. It has long been known that stimulation of the sympathetic nerves increases the rate of flutter induced by faradization.[31b] With aconitine-induced flutter it may increase the rate

30. Lewis, T.; Drury, A. N., and Iliescu, C. C.: The State of Rapid Re-Excitation of the Auricles, Heart **8**:311 (Aug.) 1921.

to the point of fibrillation.[31] Fibrillation appeared as soon as the rate reached values of approximately 600; after the end of the stimulation of the sympathetic nerves, flutter reappeared as soon as the rate reached 600 again.

Following atropinization, sympathetic stimulation did not influence the rate of the basic rhythm.[31] The latter was thought to be auricular flutter, but new studies create doubt whether flutter actually exists after atropinization, since a sinus tachycardia with a rate of 250 seems more likely.

The increased rate before atropinization may be due to a direct action of the sympathetic nerves or may be due to a reflex increase of vagus tonus. Simultaneous excitation of vagus fibers, in spite of the use of shielded electrodes, also has to be considered. These experiments need reinvestigation.

The effects of epinephrine and arterenol (nor-epinephrine) on the elements of myocardial action (membrane polarization, action current, refractory phase, etc.) have not yet been adequately studied. Nor do we know much about the effects of sympathicolytic substances in this regard. Very contradictory findings are available about the effect of the sympathetic nerves and epinephrine on the refractory phase.

AURICULAR FIBRILLATION, UNIFOCAL OR MULTIFOCAL

The topical application of aconitine to the dog auricle leads to auricular fibrillation, which stops when the treated spot is cooled. Obviously, this fibrillation is dependent on a single tachysystolic center (center of rapid stimulus formation). If the aconitine should reach other parts of the auricle, either by spillage, diffusion, or accidental injection into the blood stream, then the fibrillation does not stop when the original site of application is cooled.[32] The aconitine has set up other, more distant, centers, which maintain the fibrillation.

Auricular flutter caused by faradization is readily stopped by cooling the faradized site.[33] When faradization induces auricular fibrillation, then cooling of the faradized site rarely stops it, particularly if vagomimetic substances are used simultaneously. Similarly, when the topical application of acetylcholine induces fibrillation the cooling of the treated spot has no effect. However, fibrillation caused by either faradization or acetylcholine can be stopped by cooling the sinus and auriculoventricular nodes simultaneously. In the acetylcholine-induced type fibrillation reappears immediately on cessation of the cooling.[32a] It is clear that in these experiments the fibrillation was sustained by more than one center. Furthermore, one can state definitely that these centers were located in the sinus and auriculoventricular nodes.

The following experiment shows that fibrillation induced by acetylcholine can be sustained by the auriculoventricular node alone. Acetylcholine was applied

31. Scherf, D.: The Effect of Sympathetic Stimulation on Auricular Flutter, Am. Heart J. **37**:1069 (June) 1949.

32. (*a*) Scherf, D.; Morgenbesser, L. J.; Nightingale, E. J., and Schaeffeler, K. T.: Further Studies on Mechanism of Auricular Fibrillation, Proc. Soc. Exper. Biol. & Med. **73**:650 (April) 1950. (*b*) Scherf.[1b]

33. (*a*) Brown, B. B., and Acheson, G. H.: Aconitine-Induced Auricular Arrhythmias and Their Relation to Circus-Movement Flutter, Circulation **6**:529 (Oct.) 1952. (*b*) Prinzmetal, M.; Corday, E.; Oblath, R. W.; Kruger, H. E.; Brill, I. C.; Fields, J.; Kennamer, S. R.; Osborne, J. A.; Smith, L. A.; Sellers, A. L.; Flieg, W., and Finston, E.: Auricular Flutter, Am. J. Med. **11**:410 (Oct.) 1951. (*c*) Scherf.[1b]

topically to a spot near the sinus node, and fibrillation appeared. The sinus node and the treated spot were isolated from the rest of the auricles by clamps. The fibrillation persisted without any apparent change. Then the auriculoventricular node was cooled by lifting the heart from its pericardial bed and applying the thermode through the inferior vena cava to the auriculoventricular node. Thereupon, fibrillation stopped immediately and auriculoventricular rhythm appeared. On cessation of cooling the fibrillation reappeared; this sequence could be executed repeatedly. Thus, auricular fibrillation can be maintained by centers in the auriculoventricular node (Fig. 6).

Auricular fibrillation induced by the focal application of acetylcholine deserves additional comment. Its characteristic feature is that the fibrillation is rarely stopped if the treated area is cooled or isolated from the rest of the auricle about 20 seconds after the strictly local application. In this, it contrasts sharply with the aconitine-

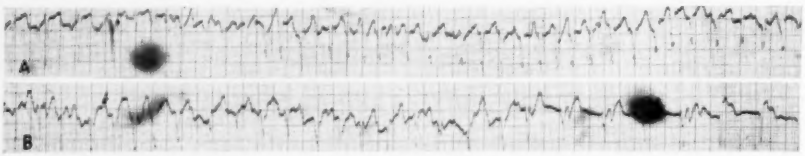

Fig. 6.—*A*, the beginning of Figure 6*A* shows auriculoventricular rhythm which had appeared in a dog after the sinus node was clamped off. Inverted P waves are visible before each QRS complex. Injection of acetylcholine into the muscle fibers of the wall of the right auricle causes auricular fibrillation. *B*, cooling of the auriculoventricular node in the manner described in the legend to Figure 4 abolished the fibrillation and the auriculoventricular rhythm reappeared, in which negative P waves follow each QRS complex. After interruption of the cooling, two inverted P waves follow a QRS complex in flutter rate and then fibrillation reappears (Lead II).

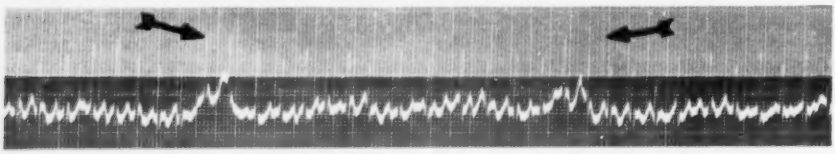

Fig. 7.—Tracing shows auricular fibrillation in a dog, following application of a piece of filter paper about 4 sq. mm. in size, moistened with acetylcholine, to the appendix of the right auricle. As soon as auricular fibrillation set in, the whole appendix was clamped off from the rest of the auricle. Contrary to the experience with aconitine-induced fibrillation, clamping remained without effect (Lead II). The arrows indicate the application and removal of the clamps, respectively.

induced fibrillation. Often, even immediately after the topical application of acetylcholine, clamping and cooling are ineffective (Fig. 7). This rules out the possibility mentioned by Dawes [34] that diffusion of the locally applied acetylcholine is responsible. There is no evidence that the drug can diffuse with such rapidity from the site of its topical application. It is conceivable that the drug may cause a reflex vagal stimulation which might affect the sinus and auriculoventricular nodes.

Thus, it is justified to differentiate two forms of auricular fibrillation, one with a single focus and one with multiple tachysystolic sustaining foci. As far as inspec-

34. Dawes, G. S.: Experimental Cardiac Arrhythmias and Quinidine-like Drugs, Pharmacol. Rev. **4**:43 (March) 1952.

tion and the electrocardiogram are concerned, the two types appear to be alike. Only after an attempt is made to arrest the fibrillation by inhibiting a known center can a given case be classified as unifocal or multifocal.

The terms unifocal and multifocal refer to the number of self-sustaining tachysystolic centers; these are centers which can maintain fibrillation for a prolonged time. As will be explained below in the Comment, the fibrillating state is characterized by the presence of many tachysystolic centers.

In the auricle, both faradization and the topical application of acetylcholine induce self-sustaining tachysystolic centers which are found at a considerable distance from the treated site. The new centers appear to lie in the sinoauricular and auriculoventricular nodes. It is not clear why aconitine does not induce such centers. Essential for the establishment of such self-sustaining tachysystolic centers is the bombardment with rapid stimuli which emanate from the treated site. If the fibrillation induced by the topical application of aconitine is allowed to persist for even as long as 20 minutes, the arrhythmia is still stopped by inhibition of the treated site. By this time there should have been ample opportunity for the rapid stimuli from the aconitinized center to induce self-sustaining tachysystolic centers in the specialized tissues if rapid bombardment were the only prerequisite. Apparently other factors are involved. The following are known to facilitate the inception of tachysystolic centers: vagal stimulation, stretching of the myocardium, and crushing injuries. Atropine diminishes the tendency toward repetitive firing of a center with the heart in situ.

It is possible that faradization of the auricles or the topical application of acetylcholine causes a vagal stimulation of the nodal tissues, so that the combination of bombardment with rapid stimuli plus vagal effect induces sustained tachysystolic centers in the distant nodes.

There appear to be transitional forms between the unifocal and multifocal types of auricular fibrillation. Occasionally topical application of acetylcholine induces fibrillation which is stopped by cooling only the treated area. On the other hand, in some experiments prolonged cooling or clamping of an aconitinized site is required to stop the fibrillation.[32] This indicates that other tachysystolic centers have maintained the fibrillation for an appreciable period.

MECHANISM OF AURICULAR FLUTTER INDUCED BY CRUSHING AND ELECTRIC STIMULATION

Faradization or stimulation of the dog auricle by rapid electrical shocks elicits persistent flutter only occasionally and fibrillation more rarely. Rosenblueth and Garcia Ramos found that more persistent flutter could be induced if faradization was combined with crushing of the auricular muscle between the venae cavae.[2] These authors believe that the mechanism is a circus movement. The crushing compels the circus wave to travel around the orifices of both venae cavae and not around each vein. Some of their experimental results are interpreted as speaking strongly in favor of a circus movement. Thus, they report that crushing additional parts of the auricular muscle elsewhere does not modify the rate of the existing flutter, whereas crushing the areas adjacent to those originally crushed slows the flutter rate. They believe this indicates that the path of the circulating wave has been lengthened. Further investigation of this phenomenon is certainly indicated.

It can be confirmed that after crushing of auricular muscle in the area described, faradization of the auricle is often, but not always, followed by more prolonged flutter than in the intact auricle. We could, however, observe the same effect after crushing other areas of the auricle distant from the muscle bundles between the venae cavae. There are objections to the concept that this type of flutter is due to a circus mechanism. Lewis postulated, and his experiments were intended to prove, the existence of a path of the circus wave around the venae cavae when the muscle was not crushed. The region crushed contains elements of the sinoauricular node. It is conceivable that damaged specialized tissue is more susceptible to development of a center of rapid stimulus formation upon electrical stimulation. We could always stop the flutter induced by crushing and faradization by cooling the crushed area (Fig. 8). This observation and the slowing of the flutter rate preceding the reappearance of sinus rhythm are better understood if one assumes the presence of an ectopic focus. If during this type of flutter a broad ligature was applied around the taenia terminalis and neighboring tissue, the flutter continued without any change. It should have been terminated immediately if the circular path around the veins were essential.

Certain differences between the flutter caused by aconitine and that appearing after crushing have been reported.[33a]

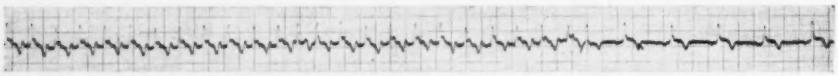

Fig. 8.—Auricular flutter with a rate of 374 and a 2:1 block in a dog, after crushing of the muscle bundles connecting both venae cavae and faradization. Cooling shows the auricular rate to 313, and the flutter suddenly stops (Lead II).

With the evidence available at this time, the experiments of Rosenblueth and Garcia Ramos cannot be accepted as proof for the existence of a circus movement during auricular flutter.

OTHER PERTINENT EXPERIMENTS

Prinzmetal and his colleagues have repeated our experiments and confirmed our results.[35] Unfortunately, they have not acknowledged our previous work adequately, and so the erroneous impression has arisen that they were the first to demonstrate with the topical aconitine method that the mechanism of flutter and fibrillation is rapid stimulus formation in the aconitine-treated area.

High speed cinematographic pictures were taken during auricular flutter caused by our aconitine method. The authors claim that the moving pictures show the absence of a circulating wave. We agree with Dawes [34] that a circulating wave in a small muscle mass need not cause a contraction that would be visible in moving pictures.

The electrocardiograph records made by these authors, which were taken during auricular fibrillation, with direct leads, considerable amplification, and a cathode

35. Prinzmetal, M.; Corday, E.; Brill, I. C.; Oblath, R. W., and Kruger, H. E.: The Auricular Arrhythmias, Springfield, Ill., Charles C Thomas, Publisher, 1952. New Light on the Mechanism of Auricular Arrhythmias, Editorial, Ann. Int. Med. **33**:486 (Aug.) 1950. Prinzmetal.[33b] Prinzmetal.[9]

ray oscilloscope, show significant findings. They reveal the presence of minute (M) waves and large (L) waves. The former occur at rates as fast as 40,000 times per minute and their voltage is between 0.05 and 0.5 millivolts. They are not registered in the usual electrocardiogram. The L waves are like flutter waves but are very irregular. Their rate is between 400 and 1,000 times per minute and their voltage lies between 3 and 10 millivolts. These waves are registered as the F waves in the usual electrocardiogram. Between the M and L waves are waves of all sizes and rates. These authors do not attempt to integrate these different waves into the theory of fibrillation. The possible significance which we attach to them is discussed in the Comment.

VENTRICULAR FLUTTER AND FIBRILLATION

Most of the theories of the mechanism of fibrillation were based on studies of ventricular fibrillation. The ventricular form was known earlier; it was more easily induced, and its dramatic lethal qualities attracted attention. Therefore earlier investigators concentrated on it more than on the auricular form.

No one has claimed an actual demonstration of a circus movement in ventricular fibrillation. Lewis stated that the electrocardiographic pictures of the auricular and the ventricular form are so similar that conclusions drawn from one would be valid

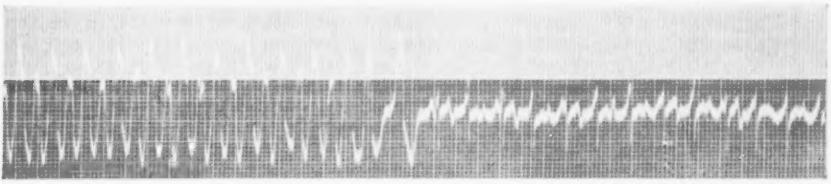

Fig. 9.—Auricular flutter in a dog after topical application of aconitine. Topical application of aconitine to the conus area of the right ventricle causes a ventricular tachycardia with a rate of 375 beats per minute. Cooling of the area on the ventricle on which aconitine had been applied slows the rate and the ventricular tachycardia (flutter) disappears. Four to five seconds after discontinuation of the cooling the ventricular tachycardia recurs.

for the other.[6] The chief evidence available for the circus movement is found in Garrey's experiments. He noted that fibrillation could be induced more readily in larger muscle masses than in smaller. This finding could be interpreted also to fit the ectopic-focus theory. Larger muscle masses facilitate the induction of several centers because the specialized tissue is present in larger amounts. It has been definitely established that the specialized fibers have a greater propensity for repetitive response.

If a few crystals of aconitine are applied to any point of the dog ventricle, a ventricular tachycardia appears within one to three minutes with a rate of 300 to 370. Since this tachycardia resembles in all details the auricular flutter, is elicited in the same manner, and is also followed by fibrillation, we may call it ventricular flutter.[36] Invariably it can be slowed or stopped by cooling the spot on which aconitine has been applied (Fig. 9). As soon as the cooling is discontinued, the rate returns to its original speed. Such findings speak strongly against the presence of

36. Scherf, D.; Morgenbesser, L. J.; Nightingale, E. J., and Schaeffeler, K. T.: Mechanism of Ventricular Fibrillation, Cardiologia **16**:232, 1950.

a circus movement. At best, one would have to assume a circus movement in a small area, of 2 to 3 mm. across; this could exist only if the rate were a multiple of that actually found. Furthermore, cooling should not slow the rate; it should only stop the arrhythmia if a circus mechanism prevailed. The experiment is good evidence for the ectopic-focus theory.

The flutter often changed suddenly into fibrillation. From this moment on, cooling was ineffective. Even cooling large areas of the ventricles did not modify the fibrillation. As is well known for other forms of experimental ventricular fibrillation, it is necessary to inhibit the entire ventricular myocardium to stop it. Even if the ventricles are cut into several pieces, these continue to fibrillate.

In explanation, the following sequence may be proposed: The topical application of aconitine on the ventricle induces a tachysystolic focus (flutter) locally. The ensuing bombardment of rapid stimuli induces the formation of innumerable tachysystolic centers in all parts of the ventricular myocardium. The simultaneous activity of these tachysystolic centers is seen as fibrillation. In contrast to the auricular fibrillation induced by topical application of aconitine, but similar to that induced by faradization or topical application of acetylcholine, the recruited ventricular tachysystolic centers are self-sustaining. Accordingly, after they have been induced,

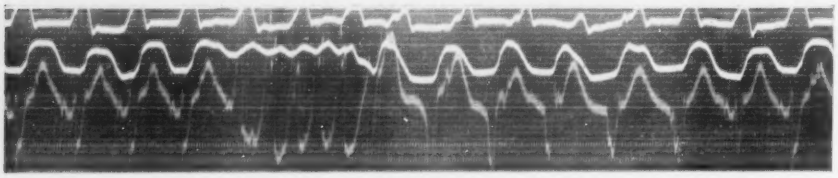

Fig. 10.—Tracing from a dog heart. From above downward as follows: signal of electrical stimulation, suspension curves of right auricle and right ventricle, electrocardiogram in ano-esophageal lead, and time base (0.02 second). The left bundle branch had been severed a few minutes earlier. Quinine dihydrochloride (0.1 gm.) had been given intravenously just before the tracing was taken, in order to prevent ventricular fibrillation, which otherwise usually follows stimulation of the ventricle with rapid and strong induction shocks. The action of the quinine explains the form of the P waves and QRS complexes. At first, four sinus beats appear. As the signal at the top of the tracing indicates, induction shocks were applied to the conus of the right ventricle, and five right ventricular extrasystoles appear. They are followed by a series of six ectopic beats originating in the left ventricle.

the inhibition of the original aconitinized center is without effect. In contrast to the limited number of sustaining foci in multifocal auricular fibrillation, ventricular fibrillation has innumerable sustaining foci.

There is other evidence that in the ventricles rapid stimulation of the centers awakens sustained repetitive action. Electrical or mechanical stimulation of the ventricles leads to long chains of ectopic beats, which usually originate in the stimulated area.[37] Occasionally, however, the centers are awakened elsewhere, even in the contralateral ventricle (Fig. 10).

These experiments indicate that the ventricular myocardium has a propensity for developing sustained repetitive activity.

37. Scherf, D.: Zur Enstehungsweise der Extrasystolen und der extrasystolischen Allorhythmien, Ztschr. ges. exper. Med. **51**:816 (June) 1926.

Wiggers and his collaborators [38] found that a very rapid series of ectopic beats are an indispensable factor for the appearance of ventricular fibrillation. He felt that they resulted in the development of block areas and a reentry mechanism. We prefer to explain ventricular fibrillation as the development of many tachysystolic foci causing the presence of several activation waves simultaneously in the heart. If some local reentry waves appear, they are the consequence and not the cause of the mechanism of fibrillation.

COMMENT

The available evidence indicates clearly that flutter and fibrillation originate in one or more local areas. As yet there is no definite demonstration that a circus movement has been responsible for any type of cardiac flutter and fibrillation. Neither Garrey nor Lewis nor Rosenblueth and Garcia Ramos has proved the existence of a circus movement completely, even in one instance. The evidence they present can easily fit the framework of the ectopic-focus theory.

All the known forms of cardiac flutter and fibrillation can be explained by the ectopic-focus theory. The differences between the known forms depend on the number of ectopic tachysystolic foci and on their persistence. Thus, in the auricular fibrillation induced by the topical application of aconitine, the inhibition or isolation of the treated spot usually stops the fibrillation because other topical centers have little tendency toward self-perpetuation. On the other hand, when acetylcholine is applied inhibition of the original site does not stop the arrhythmia. The propensity for sustained repetitive firing is enhanced by acetylcholine; hence tachysystolic centers arise in the sinus and auriculoventricular nodes. To control the fibrillation it is necessary to inhibit the latter centers also.

There are cases which are transitional between the unifocal and multifocal types of auricular fibrillation. Thus, when the aconitine site is inhibited the auricular fibrillation may persist for a minute or two. On the other hand, when the acetylcholine site is inhibited the fibrillation occasionally stops immediately.

There does not seem to be a unifocal type of ventricular fibrillation. It is possible that the anoxia which immediately accompanies ventricular fibrillation increases the tendency toward persistent activity of the recruited tachysystolic centers.

In what does fibrillation differ from a regular tachycardia-like flutter? Obviously it is not an extreme form of flutter, for when flutter accelerates into fibrillation something new is suddenly added to or replaces the regular tachycardia emanating from a tachysystolic focus. The character of the latter, the instigating focus, has not been lost completely, because in the case of the aconitine-induced auricular fibrillation its inhibition stops the fibrillation.

Is the characteristic activity of the fibrillating myocardium due to the presence of a rapidly firing center plus the appearance of islands of refractory tissue? This concept was considered by Porter [39] and elaborated in classic investigations by Lewis and his school. As evidence, it has been demonstrated repeatedly that inductibility of fibrillation parallels the retardation of myocardial conduction—that is to

38. Wiggers, C. J.: The Mechanism and Nature of Ventricular Fibrillation, Am. Heart J. **20**:399 (Oct.) 1940. Moe, G. K.; Harris, A. S., and Wiggers, C. J.: Analysis of the Initiation of Fibrillation by Electrographic Studies, Am. J. Physiol. **134**:473 (Oct.) 1941.

39. Porter, W. T.: On the Results of Ligation of the Coronary Arteries, J. Physiol. **15**:134, 1894.

say, the slower the myocardial conduction, the easier it is to induce fibrillation. However, the two factors may be related to common causes and not to each other. The role played by "block areas" can, however, not be evaluated as yet with certainty.

We propose to define the characteristic activity of fibrillation in another manner, one more consistent with recent observations. Registration from the fibrillating auricular myocardium [36] reveals that all parts are in action. Stimuli are emanating from all parts, and not from any one part. The larger activation waves, the L waves, which correspond to the coarse F waves, have all the earmarks of chance summation of haphazardly propagated impulses. However, in addition, and most important for the theory, is the ubiquity of the minute (M) waves. Their potentials are so small and their rate so fast that they cannot be due to propagated impulses. They must arise in situ. They are similar to the local potentials or prepotentials that have been registered from nerves which were stimulated by subliminal shocks [40] or from injured muscle fibers.[41] They have also been found to occur spontaneously and thus can be classified as nonpropagated subliminal stimuli. They cannot be explained by a simple combination of rapid stimuli and refractory islands. They can be explained only as minute tachysystolic centers which were induced by the bombardment of rapid stimuli from a distant focus. The L and M oscillations appear to arise in all parts of the myocardium. They probably have few sustaining qualities. Once the sustaining pacemakers are inhibited, the oscillations die out. If one or more self-sustaining tachysystolic centers are induced in a given case of fibrillation, they probably lie in specialized tissue (probably in the Purkinje fibers). Because they are propagated, their oscillations must of necessity be of the large (L) type.

Accordingly, the characteristic feature of fibrillation seems to be repetitive action. With the onset of fibrillation, initiated in some way by a tachysystolic center, the myocardium starts to show repetitive action in all its parts in a totally irregular manner. This action consists of spontaneously formed oscillations of potential, whose size and rate range from the coarse F waves to the minute M waves, with all gradations between.

As with stimulus formation in general, the mechanism of repetitive action is unknown. However, from electrophysiological experiments with nerves and muscles much is known of the factors which favor its appearance. It is facilitated by calcium lack and anodal polarization (analectrotonus). It is most easily elicited by stimulating a nerve or muscle preparation with a series of rapid electrical shocks. It can also be induced by a single electrical or mechanical shock or by a constant electrical or chemical stimulus. The repetitive action in such cases appears as a series of impulses which arise after the cessation of the original stimulus. This is called repetitive response. It has been observed in the myocardium [37] and has become an important feature in the explanation of various cardiac arrhythmias.[42] The specialized fibers of the heart are well known for their propensity to repetitive action. Normally, a single stimulus reaching a conduction fiber results in a single action

40. Hodgkin, A. L.: The Local Electric Changes Associated with Repetitive Action in a Non-Medullated Axon, J. Physiol. **107**:165 (March) 1948.

41. Bozler, E.: The Initiation of Impulses in Cardiac Muscle, Am. J. Physiol. **138**:273 (Jan.) 1943.

42. Scherf, D., and Schott, A.: Extrasystoles and Allied Arrhythmias, London, William Heinemann, Ltd.; New York, Grune & Stratton, 1953.

potential. Sometimes the single stimulus causes the fiber, if it is altered in some way, to form rapid oscillating potentials. If the latter are large enough they are propagated and cause an activation of the entire heart. This sequence is the basis for the most likely explanation for the occurrence of extrasystoles and their dependence on the preceding beat (fixed coupling).[42]

Since inhibition of the original center plus the induced centers in the specific nodes stops auricular fibrillation, it is reasonable to believe that the repetitive action is nonpersistent in the rest of the fibrillating myocardium. The continuation of a constant state of activity depends on the centers of specific tissue. In contrast, in the ventricular form of fibrillation the repetitive action is persistent in innumerable centers throughout the myocardium, since specialized fibers are present in all parts. Thus, it is not possible to stop the fibrillation by inhibiting a few select centers.

We know nothing of the mechanism whereby rapid bombardment of stimuli induces repetitive action in the myocardium.

In spite of the absence of direct evidence for the mechanism of flutter and fibrillation in man, it is reasonable to ascribe to them the mechanisms found in the experimental animal; the electrocardiographic picture and the pharmacological responses of human arrhythmias are the same as those seen in animals.

The objection is often raised that the assumption of an ectopic focus as the cause of flutter or fibrillation requires an explanation of how one cardiac center is able to form so many rapid stimuli over many years. Such rates are known, however, in several mammals. Thus, the heart rate of the mouse exceeds 600 per minute, and that of the bat, 900.

Usually a distinction is made between paroxysmal tachycardia and flutter. Clinically, it is customary to apply the label of tachycardia to a rapid regular heart action which is readily stopped by vagal stimulation. Flutter is considered to be a precursor of fibrillation, to have a more rapid rate, and to show continuously undulating F waves. Vagal stimulation has no effect on it.

On the basis of experimental evidence it seems that both are the consequence of rapid stimulus formation in a focus. It appears that the undulations of the F waves in the electrocardiogram are only the consequence of the rapid rate. Experimentally, vagal stimulation may stimulate or inhibit high rates as well as slow one.[26c] The rate of auricular flutter during quinidine administration may be as low as 160 beats per minute. Clinically, however, as far as we know a rapid auricular flutter has not been stopped by vagal stimulation. A possible exception is an observation of an auricular tachycardia with a rate of 250, which may well have been flutter.[43]

In our opinion, it is premature at present to abandon the differentiation between these two forms of auricular tachycardia. In spite of the demonstrable presence of a single tachysystolic focus in both, the finer mechanisms of stimulus formation may yet be shown to be different.

Fibrillation, however, which was hitherto considered to be closely related to flutter, appears to differ fundamentally by virtue of the presence of numerous tachysystolic foci.

43. Wilson, D. C.: The Value of Vagal Stimulation in Paroxysmal Auricular Tachycardia as Illustrated in an Unusual Case, Heart **8**:303 (Aug.) 1921.

SUMMARY AND CONCLUSIONS

The different theories of the mechanism of flutter and fibrillation are discussed. Recent personally conducted experiments are described, which are based on our aconitine method. They convincingly demonstrate that these arrhythmias arise from circumscribed tachysystolic centers. The circus-movement theory in any of its forms is unable to account for the findings.

The effects of vagal and sympathetic stimulation are described for both experimental and clinical types of flutter and fibrillation. The experimental findings correlate well with the known action of vagus stimulation on the individual myocardial fiber. However, in clinical cases the correlation is poor. The effect of sympathetic stimulation requires further study.

A theory of fibrillation is proposed whereby the state of fibrillation is characterized by the presence of innumerable tachysystolic centers of both large and small degree. The theory is based on the presence of minute electrical oscillations in fibrillating muscle. They are small, rapid, and ubiquitous and therefore not manifestations of conducted impulses. They must arise in situ, and they thus constitute tachysystolic foci. Thus there are tachysystolic foci of all sizes throughout the fibrillating myocardium; some are propagated, others remain local. Their understanding is facilitated by reference to similar well-known phenomena in other fields of electrophysiology. They can be given the generic label of repetitive action.

These tachysystolic centers die out, for the most part, when the sustaining centers are inhibited. The latter are also tachysystolic centers but they have the ability to maintain themselves (and also the fibrillation) for prolonged periods.

Fibrillation can be classified according to the number of sustaining centers present. Thus, the fibrillation induced by the topical application of aconitine is unifocal, for when the aconitinized site is inhibited the fibrillation stops. On the other hand, faradization or the topical application of acetylcholine results in a multifocal type of auricular fibrillation. Here sustaining centers have been induced not only at the site of application but also in the sinoauricular and auriculoventricular nodes. To stop the fibrillation it is necessary to inhibit all three sites. Ventricular fibrillation is a multifocal type, with innumerable sustaining centers which are located probably in the Purkinje fibers. The entire myocardium must be inhibited to stop the fibrillation.

Progress in Internal Medicine

INFECTIOUS DISEASES

Eighteenth Annual Review of Significant Publications

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DURING the past year, as usual, contributions to knowledge in the field of infectious disease covered a wide variety of interests. Antibiotic and chemotherapeutic agents were the subjects of most importance. Further evaluation of dosage and of the therapeutic effects were made of agents now available, and new antibiotics were introduced. Studies are in progress to test the value of newly introduced chemical compounds for the treatment of tuberculosis, malaria, amebiasis, and other diseases. Much attention was given to the untoward results of therapy with antibiotics, such as toxic or allergic reactions and the replacement of antibiotic-sensitive microbes with antibiotic-resistant ones. Retrospective investigation revealed the cause of a number of puzzling epidemics of pneumonia and others of encephalitis observed several years ago. The value of prophylactic vaccination against rabies was questioned. Large-scale projects are under way in many countries to vaccinate against tuberculosis. In the United States gamma globulin was tested as a possible preventive agent against poliomyelitis. Interest in the effects of adrenocorticotropic hormones on infection seems to have waned.

ANTIBIOTICS

A year or two ago warning was given of the danger of masking or temporarily suppressing unrecognized early syphilis in patients treated for gonorrhea with relatively small doses of penicillin. Later experimental studies indicate that minimal amounts of penicillin given during the incubation period of syphilis actually may be curative.[1] The widespread use of penicillin given for various other diseases may incidentally cure many early undiagnosed syphilitic infections. The apparent decline in the incidence of syphilis may be due more to this cause than to the treatment and cure of the recognized disease.

Aureomycin successfully controlled all but 12 of 47 instances of surgical infections. Oxytetracycline ("terramycin") gave satisfactory results in the treatment of cellulitis, bacteremia, and peritonitis, except in the case of antibiotic-resistant bacteria.[2] While the administration of penicillin or streptomycin lowered the mor-

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1. Hollander, D. H.; Turner, T. B., and Nell, E. E.: Effect of Long Continued Subcurative Doses of Penicillin During the Incubation Period of Experimental Syphilis, Bull. Johns Hopkins Hosp. **90**:105-121 (Feb.) 1952.

2. Pulaski, E. J.; Artz, C. P. and Reiss, E.: Terramycin and Aureomycin in Surgical Infections: Report of 200 Cases, J. A. M. A. **149**:35-40 (May 3) 1952.

tality rate for perforation and peritonitis resulting from appendicitis induced experimentally in rabbits, antibiotic therapy should not be used alone in the treatment of appendicitis and its complications.[3]

Neomycin employed topically was found to be the antibiotic of choice in the treatment of cutaneous pyogenic infections unless hemolytic streptococci are the cause.[4] In that case, bacitracin is preferable. Aureomycin is as effective as streptomycin in inducing remissions in tularemia, but the curative value of streptomycin is greater.[5] Rhinoscleroma caused by Klebsiella rhinoscleromatis was successfully treated with streptomycin,[6] and antibiotics are preferable to sulfonamide compounds for trachoma.[7] Aureomycin, chloramphenicol, and oxytetracycline are ineffective in the treatment of viral hepatitis.[8]

Ninety-one patients with pneumonia were treated with oxytetracycline.[9] The agent was effective against pneumococcic pneumonia and gave "immediate effects" in pneumonias of undetermined origin and in four cases of viral pneumonia. However, in many patients staphylococci replaced the flora in the sputum and caused serious, occasionally fatal, secondary infections in the lung and in the colon. Seven patients died, and in five the gastrointestinal disturbance caused by oxytetracycline may have been partly responsible for the outcome. Penicillin still is the agent of choice for the treatment of pneumococcic pneumonia.

Prodigiosin was used for the treatment of coccidioidomycosis.[10] The condition of five patients was considered hopeless; of the nine others, three seemed to have recovered and the rest were not improved. Further observations are necessary to determine the value of antibiotic therapy for mycotic diseases.

Indiscriminate Use and Untoward Effects.—The 16 commercial manufacturers of antibiotics in the United States have reached an astounding production rate monthly of 24 tons of aureomycin, chloramphenicol, and oxytetracycline; 21 tons of streptomycin, and 30 tons of penicillin.[11] In view of the comparatively small percentage of infections which are amenable to therapy with antibiotics, one wonders for what purposes most of these enormous amounts are used. Probably about 90% of antibiotics used therapeutically at present are wasted chiefly (*a*) on

3. Toon, R. W., and Wangensteen, O. H.: Effect of Antibiotics on Obstructive Peritonitis in Rabbits, Proc. Soc. Exper. Biol. & Med. **80**:578-580 (Aug.-Sept.) 1952.

4. Livingood, C., and others: Pyogenic Infections Treated with Neomycin, J. A. M. A. **148**:334-339 (Feb. 2) 1952. Kile, R. L.; Rockwell, E. M., and Schwarz, J.: Use of Neomycin in Dermatology, ibid. **148**:339-343 (Feb. 2) 1952.

5. Corwin, W. C., and Stubbs, S. P.: Further Studies on Tularemia in the Ozarks: Review of 44 Cases During a 3 Year Period, J. A. M. A. **149**:343-345 (May 24) 1952.

6. Russell, D. A.; Moore, J. M., and Mattman, L. H.: Rhinoscleroma Successfully Treated with Streptomycin, J. A. M. A. **148**:642-643 (Feb. 23) 1952.

7. Siniscal, A. A.: The Sulfonamides and Antibiotics in Trachoma, J. A. M. A. **148**:637-638 (Feb. 23) 1952.

8. Colbert, J. W.; Bungards, L., and Knowlton, M.: Aureomycin, Chloromycetin and Terramycin in Treatment of Acute Viral Hepatitis, Proc. Soc. Exper. Biol. & Med. **79**:339-343 (March) 1952.

9. Jackson, G. G., and others: Terramycin Therapy of Pneumonia: Clinical and Bacteriologic Studies in 91 Cases, Ann. Int. Med. **35**:1175-1202 (Dec.) 1951.

10. Wier, R. H., and others: A Clinical Trial of Prodigiosin in Disseminated Coccidioidomycosis, Am. J. M. Sc. **224**:70-76 (July) 1952.

11. Erythromycin—A New Broad Spectrum Antibiotic, Editorial, Antibiotics & Chemother. **2**:279-280 (June) 1952.

diseases known to be uninfluenced by them, particularly minor infections of the respiratory tract; (*b*) in unnecessarily large dosage "just to be sure;" (*c*) in needlessly prolonged therapy; (*d*) in unnecessary combinations of antibiotics; (*e*) in topical applications, and (*f*) for illogical prophylactic purposes. The matter of indiscriminate use would not be so serious if only financial expense were involved, but a number of harmful aspects aside from hypersensitivity may be mentioned, as in the following paragraphs.

Toxicity.—Twenty-nine cases of aplastic anemia, many of them fatal, occurring after therapy with chloramphenicol are described in three papers in the July 5, 1952, issue of *The Journal of the American Medical Association* and two papers of the Aug. 2 issue of the same journal. The antibiotic seemed to be the cause, although in some cases the disease itself or other administered drugs may have participated. The hazard of causing aplastic anemia or granulopenia would seem to restrict the use of chloramphenicol to the treatment of typhoid, against which other antibiotics are ineffective.

Mycotic Infections.—As previously mentioned, antibiotic therapy may induce replacement of the natural bacterial flora with staphylococci. Fungi also are implicated, but a question arises as to whether they are pathogenic and invasive or are present as saprophytes on tissue injured by other factors. The subject was discussed editorially.[12] According to some observers, neither a deficiency of vitamin B [13] nor suppression of bacterial growth is responsible for the growth of fungi. The host's resistance is lowered or the growth of fungi may be stimulated.[14] On the latter assumption the administration of parahydroxybenzoic acid was proposed to suppress the growth of fungi during therapy with broad-spectrum antibiotics.[15]

According to Kligman the importance of mycotic overgrowth during antibiotic therapy is exaggerated.[16] He was unable to demonstrate an increase in the growth of Candida albicans from exposure to antibiotics. Most of the reported instances of mycoses after antibiotic therapy are not examples of the invasion of pathogenic fungi. The mere presence of fungi, even in large numbers, does not prove their pathogenicity. Many instances reported as pulmonary moniliasis merely represent the growth of C. albicans on tissue injured by other factors. Therapy with antibiotics, especially if prolonged, no doubt has increased the incidence of candidosis (moniliasis), but the mold is a saprophyte and in only rare instances is it able to cause systemic disease. Mycotic endocarditis after therapy with penicillin [17] and mycotic granuloma of the spinal cord after intrathecal injection of penicillin were recorded.[18]

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12. Fungus Infections Complicating Antibiotic Therapy, Editorial, J. A. M. A. **149**:762-763 (June 21) 1952.

13. Tomaszewski, W.: Findings from Lingual Scrapings Taken During Treatment with Chloramphenicol and Aureomycin, J. Clin. Path. **4**:393-401 (Nov.) 1951.

14. Seligmann, E.: Virulence Enhancing Activities of Aureomycin on Candida Albicans, Proc. Soc. Exper. Biol. & Med. **79**:481-484 (March) 1952.

15. McVay, L. V., Jr., and Sprunt, D. H.: A Study of Moniliasis in Aureomycin Therapy, Proc. Soc. Exper. Biol. & Med. **78**:759-761 (Dec.) 1951.

16. Kligman, A. M.: Are Fungus Infections Increasing as a Result of Antibiotic Therapy? J. A. M. A. **149**:979-983 (July 12) 1952.

17. Kunstadter, R. H.; MacLean, H., and Greengard, J.: Mycotic Endocarditis Due to Candida Albicans, J. A. M. A. **149**:829-832 (June 28) 1952.

18. Wybel, R. E.: Mycosis of Cervical Spinal Cord Following Intrathecal Penicillin Therapy: Report of a Case Simulating Cord Tumor, A. M. A. Arch. Path. **53**:167-173 (Feb.) 1952.

A similar problem pertains to Pseudomonas (pyocyanea) and Proteus bacilli.[19] Evidence suggests an increasing number of infections caused by these bacilli in patients during antibiotic therapy. The bacilli may disappear with the cessation of therapy and the normal flora returns. Actual infection, it is said, is best controlled by treatment with streptomycin and sulfonamides for Proteus infections and with polymixin B for Pseudomonas infections. The correction of any underlying anatomic disorder is of most importance.

Other Sequels.—Pseudomembranous colitis of unknown cause may follow oral or parenteral medication with aureomycin or chloramphenicol within four days. It occurs more often in women, in a ratio to men of 3:1. Diarrhea may be absent. According to Reiner and his associates, no pathogenic bacteria or fungi have been implicated.[20] Therapy with vitamins had no effect in either prevention or cure. Other observations are recorded on about 100 patients with proctitis, pruritus, or diarrhea who had received antibiotics orally.[21] Aureomycin supposedly caused most of the disorders; oxytetracycline and chloramphenicol, the rest. The disturbances usually appeared about two weeks after therapy was begun and in some cases were more distressing than the disease for which antibiotics were given.

Indiscriminate antibiotic therapy gives rise to other unexpected circumstances. Smillie points out the desirability of accurate reporting of communicable diseases to local health authorities but fears that physicians will pay less and less attention to official regulations because of the prompt control of many infections with antibiotic therapy.[22] In a paper discussing diphtheritic paralysis, Brown reports an increasing incidence of diphtheria in Boston.[23] She believes the increase in the number of cases of paralysis to be due to the almost routine use of antibiotic agents for sore throat and the misdiagnosis of diphtheria because cultures are not made and the disease is unrecognized.

Antibiotic Antagonism.—Jawetz' view regarding the antagonism of certain antibiotic agents to each other was the subject of critical study. According to Kirby and his co-workers the matter is not of great clinical significance.[24] No interference was demonstrable in experimental studies in mice infected with hemolytic streptococci and treated with penicillin and chloramphenicol. A patient with subacute bacterial endocarditis received both penicillin and chloramphenicol and recovered.[25] No evidence of interference was observed in patients with pneumonia treated with

19. Yow, E. M.: Development of Proteus and Pseudomonas Infections During Antibiotic Therapy, J. A. M. A. **149**:1184-1188 (July 26) 1952.

20. Reiner, L.; Schlesinger, M. J., and Miller, G. M.: Pseudomembranous Colitis Following Aureomycin and Chloramphenicol, A. M. A. Arch. Path. **54**:39-67 (July) 1952.

21. Manheim, S. D.: Anorectal Complications of Aureomycin, Terramycin, and Chloromycetin Therapy, New York J. Med. **51**:2759-2760 (Dec. 1) 1951.

22. Smillie, W. G.: The Basis of Communicable Disease Control, Pub. Health Rep. **67**:287-292 (March) 1952.

23. Brown, M. R.: The Mechanism Involved in Polyneuritis as Exemplified by Postdiphtheritic Polyneuritis, Ann. Int. Med. **36**:786-791 (March) 1952.

24. Ahern, J. J.; Burnell, J. M., and Kirby, W. M. M.: Lack of Interference of Chloramphenicol with Penicillin in a Hemolytic Streptococcal Infection in Mice, Proc. Soc. Exper. Biol. & Med. **79**:568-571 (April) 1952.

25. Ahern, J. J., and Kirby, W. M. M.: Cure of Subacute Bacterial Endocarditis with Penicillin and Chloramphenicol: Report of a Treatment Resistant Case, J. A. M. A. **150**:33-35 (Sept. 6) 1952.

penicillin and aureomycin.[26] On the other hand, while combined therapy at times may be desirable, as in certain cases of resistant subacute bacterial endocarditis, it usually is better to rely on single antibiotic agents properly applied.

Effect of Antibiotic Therapy on Microbiology.—Two editorials [27] and Gocke's paper [28] are concerned with the development of resistance of bacteria to antibiotic agents. It is surprising to learn that by 1949, 86% of cases of gonorrhea failed to respond to sulfonamide therapy. At present there is alarm about the increasing incidence of infections caused by penicillin-resistant and aureomycin-resistant staphylococci. In another study nearly one-half of strains of Shigella studied resisted sulfadiazine. It seems that bacteria which become resistant to aureomycin, oxytetracycline, or chloramphenicol are resistant to all three of these antibiotics but not to streptomycin. Some bacteria at first sensitive to antibiotics later may be stimulated by them or need them for growth. Bacteria seem to defend themselves; some even are turning our weapons to their own advantage. In some instances, as mentioned before in this review, a sensitive pathogen may be eliminated by antibiotic therapy and be replaced by nonsensitive bacteria or fungi. So long as new antibiotics remain to be discovered to match the ability of bacteria to "defend themselves," their control is possible, but if, as seems to be the case, the outlook for many more new agents is not hopeful, a time may come when antibiotics are no longer of therapeutic value. Physicians are warned "not to squander our antibiotic fortune at the present prodigal rate. . . . These valuable drugs should not be hurled at the heads of each and every unidentified infection." In another provocative article, Hobby wonders what the outcome of our interference with microbial life will be.[29]

A new source of antibiotic-resistant bacteria came to light.[30] Broad-spectrum antibiotics mixed with food for poultry and livestock to increase their rate of growth may give rise to resistant strains of coliform bacilli which by way of infected eggs or meat may cause disease in man.

New Antibiotics.—Search continues for new and better antibiotic agents, but one wonders whether the end is not in sight, as seems to be the case in the field of sulfonamide compounds. Of the many thousands of antibacterial agents thus far tested, less than 10 are of enough value to be applied therapeutically. Within the year erythromycin (ilotycin®) was introduced.[31] It is a so-called broad-spectrum antibiotic derived from Streptomyces erythreus and is active against Gram-positive bacteria, and less so against Gram-negative ones but is said to be effective for

26. Kirby, W. M. M., and Ahern, J. J.: Studies of Antibiotic Antagonism, abstracted, J. Clin. Invest. **31**:643 (June) 1952.

27. Bacterial Versatility, Editorial, Ann. Int. Med. **36**:196-202 (Jan.) 1952. Cross Resistance to Antibiotics, Editorial, J. A. M. A. **148**:470-471 (Feb. 9) 1952.

28. Gocke, T. M., and Finland, M.: Cross-Resistance to Antibiotics: Effect of Repeated Exposure of Bacteria to Aureomycin, Terramycin, Chloramphenicol or Neomycin on the Resistance to All of These Antibiotics and to Streptomycin and Penicillin, J. Lab. & Clin. Med. **38**:719-735 (Nov.) 1951.

29. Hobby, G. L.: Microbiology in Relation to Antibiotics, J. Hist. Med. & Allied Sc. (No. 3) **6**:369-387, 1951.

30. Starr, M. P., and Reynolds, D. M.: Streptomycin Resistance of Coliform Bacteria from Turkeys Fed Streptomycin, Am. J. Pub. Health **41**:1375-1380 (Nov.) 1951.

31. McGuire, J. M., and others: "Ilotycin," a New Antibiotic, Antibiotics & Chemother. **2**:281-283 (June) 1952.

rickettsioses, for viral pneumonia, and for infections with corynebacteria and clostridia.[32] It is given orally and may find its use for infections which resist therapy with penicillin. Magnamyan is another newly introduced agent.[32a]

Sulfonamide Therapy.—The combination of several sulfonamide compounds once was suggested to overcome the danger of toxicity and to increase the efficiency of treatment. The logic of the idea never was clear, and subsequent study has not supported the view.[33] Mixtures of sulfonamide drugs actually may depress antibacterial activity. Single agents are preferable, and so far none has exceeded sulfadiazine in usefulness. It comes as a surprise to learn that despite their general displacement as therapeutic agents by antibiotics, sulfonamide drugs are still in increasing demand.[11] For most purposes they almost are obsolete.

DISEASES OF VIRAL OR PROBABLE VIRAL ORIGIN

Minor Infections of the Respiratory Tract.—Andrewes and his co-workers report on further transmission experiments.[34] With use of special care in isolation technique, the natural transmissibility of colds to volunteers was shown to be low. On close contact with "donors" of colds, infection developed in only 2 or 3 of 20 or 30 volunteers. The inhalation of mists was more effective, but the rate of infection rose to 50% when infected material was dropped into the nares. Apparently factors other than mere exposure to infection are needed; changing degrees of susceptibility or resistance probably are important. The virus of the cold seems to be killed by drying. Hodges [35] summarizes the problems involved and adds a table of incidence of minor respiratory tract infections, exclusive of influenza, as they affected a group of normal families in one region during a year's observation, as follows:

	No. of Illnesses	% of Total
Undifferentiated respiratory tract diseases	975	93.7
Nonstreptococcic pharyngitis	42	4.0
Streptococcic pharyngitis	14	1.4
Viral pneumonias	7	0.7
Pneumococcic pneumonia	2	0.2

It is probable that a similar distribution of diseases occurs generally. Of especial importance is the fact that only a small minority, less than 3%, are caused by agents susceptible to the effects of antibiotic therapy. If, as seems to be a current deplorable custom, antibiotics continue to be used indiscriminately for these minor infections, almost all are wasted and many persons are needlessly sensitized to them.

Another point concerns the relative incidence of streptococcic and nonstreptococcic (presumably viral) pharyngitis. If only one of every four cases of sore throat is caused by hemolytic streptococci, antibiotics or sulfadiazine obviously should not

32. Heilman, F. R., and others: Some Laboratory and Clinical Observations on a New Antibiotic, Erythromycin (Ilotycin), Proc. Staff Meet., Mayo Clin. **27**:285-304 (July 16) 1952.

32a. Tanner, F. W., and others: Some Properties of Magnamyan, a New Antibiotic, Antibiotics & Chemother. **2**:441-446 (Sept.) 1952.

33. Weinstein, L., and Murphy, E. B.: Comparison of Antibacterial Activity of Single and Combined Sulfonamides, Proc. Soc. Exper. Biol. & Med. **80**:519-522 (July) 1952.

34. Lovelock, J. E., and others: Further Studies on the Natural Transmission of the Common Cold, Lancet **2**:657-660 (Oct. 4) 1952.

35. Hodges, R. G.: Epidemiology of Upper Respiratory Tract Diseases, J. A. M. A. **147**: 1335-1336 (Dec. 1) 1951.

be given to all. It is not certain even that any therapy is of specific value in the case of streptococcic sore throat of average severity. The matter as it pertains to rheumatic fever is discussed elsewhere in this review.

It is estimated that six attacks of minor respiratory tract infection occur per person per year. It is not known whether this incidence is the result of short or weak immunity and successive attacks by the same virus or whether each attack is caused by a different virus. At any rate, there is no logic to support the use of any so-called cold vaccines for the prevention of minor infections of this nature. The failure of ultraviolet light and aerosol sprays to decontaminate air and control contagion now is well known. It appears that means other than the air-borne route convey infection from person to person. There seems to be only one procedure effective in reducing the incidence of these minor illnesses, that is, to grow older.

In experiments with volunteers (many authors habitually speak of human volunteers as if there were other kinds), Atlas succeeded in transmitting colds by the inoculation of a filtrable agent cultivated for three or four passages in the allantoic fluids of embryonated eggs.[36] The symptoms and signs were the same as those of the disease conveyed directly by inoculation of nasal washings and the same as those of the patient who served as the donor of the virus. Infection with MR-3 virus evoked resistance or immunity to homologous reinfection for eight months. Recovery from MR-3 infection failed to immunize against infection with MR-1 or MR-4 virus. Evidently different strains vary in their immunologic specificity.

In a study made in Norway of 647 soldiers with febrile catarrh, as the common cold is called, pulmonary involvement was present in 40%. It was mild in about half of the patients and would have passed unnoted without special effort to recognize it. Serologic tests showed complement-fixing antibodies for influenza virus in 1.4% of the cases and cold agglutinin in 8%, and the lygranum test gave a positive reaction in 16%.[37] As mentioned in the section on influenza, the incidence of pneumonia as recognized during influenza was considerably lower.

Influenza.—The antigenic stability of influenza viruses is a matter of controversy. According to Isaacs and Andrewes, the classic A type strains seem to have disappeared and were either replaced by other strains or were transformed into them.[38] They believe that A viruses recently supposed by others to have been derived from patients actually were "pick-ups" accidentally encountered in laboratories where these old established strains were kept in storage. Epidemics of A′ virus influenza in 1950-1951 in England probably were caused by the activation of the virus already present in different places at the same time or its importation and subsequent spread. Smith observed spontaneous mutation of virus A during routine cultural passage.[39] The altered virus was the same as the original one antigenically but had new hemagglutinative characteristics. Evidently there are variable factors

36. Atlas, L. T.: Minor Respiratory Diseases: Studies of MR-3 Virus Disease in Human Volunteers, abstracted, J. Clin. Invest. **31**:615 (June) 1952.

37. Christiansen, T., and Schmidt, V.: Pulmonary Manifestations in So-Called Catarrhal Fever: Clinical Analysis of 647 Cases, Nord. med. **45**:593-557 (April 18) 1951.

38. Isaacs, A., and Andrewes, C. H.: The Spread of Influenza: Evidence from 1950-1951, Brit. M. J. **2**:921-927 (Oct. 20) 1951. Smith, W., and others: Spontaneous Mutation of Influenza Virus A During Routine Eye Passage, Brit. J. Exper. Path. **32**:422-432 (Oct.) 1951.

39. Smith, W.; Westwood, J. C. N., and Belyavin, G.: Influenza: Study of 4 Virus Strains Isolated in 1951, Lancet **2**:1189-1192 (Dec. 29) 1951.

besides antigenic specificity. Four new strains related to A′ virus differed in susceptibility to a second, or beta, inhibitor present in rabbit serum as distinguished from the normal alpha inhibitor. The classification of influenza viruses seems to approach the complexity of that of Salmonella.

A severe epidemic reported as influenza occurred in Ecuador in November, 1951.[40] In some places 60% of the population was afflicted. The symptoms were severe, but the mortality rate was low. The incidence of pulmonary involvement was recorded in two other epidemics. In England, 17% of 223 patients with influenza had pneumonia which resisted antibiotic therapy.[41] In another study pulmonary infiltration was present in 24 of 76 patients with A′ influenza.[42] It was not affected by oxytetracycline. Involvement of the lung probably represents an integral part of influenza as a form of viral pneumonia caused by influenza virus. According to Tyrrell, pathogenic bacteria play a large part in influenzal pneumonia. In general, bacterial pneumonias are more severe if influenza also is present.[43] Report was made of the isolation of both Virus A′ and Virus C from one patient with influenza.[44] Both viruses were active in causing the disease.

Viral Pneumonia.—The relative incidence of viral pneumonia and other kinds of pneumonia varies greatly from place to place and from time to time. In Manila, Philippines, among 73 cases of pneumonia, 63 were regarded as viral and 10 as lobar.[45] In contrast, most pneumonias observed in Glasgow, Scotland, in a 15-month period were bacterial in origin, even though examination of the sputum revealed no causative organisms. Cold agglutination was observed only twice among 341 patients. The authors apparently were unable to convince themselves that viral pneumonia is of any importance.[46] Several authors who surveyed the present statistics of pneumonia seem to be unaware of the high incidence of viral pneumonias 10 years ago, when they were epidemic or pandemic. In the past few years viral pneumonias in my experience were uncommon, but it is safe to predict their resurgence in the future. Two British observers even deny the existence of viral pneumonia.[47] In a surprising paper, they try to "dispel much mysticism" and to "destroy the concept of atypical pneumonia as at present described." Because of clinical and roentgenographic similarities of the disease to aspiration pneumonia, they believe that it is not viral in origin but is caused by the aspiration of secretions during upper respiratory tract infection. Other British observers quickly refuted

40. Severe Epidemic of Influenza in Ecuador, Foreign Letters, J. A. M. A. **148**:395 (Feb. 2) 1952.

41. Fry, J.: Lung Involvement in Influenza, Brit. M. J. **2**:1374-1377 (Dec. 8) 1951.

42. Scher, J. M., and Jaruszewski, E.: Virus Influenza A′ Infection with Pulmonary Manifestations, A. M. A. Arch. Int. Med. **90**:201-216 (Aug.) 1952.

43. Tyrrell, D. A. J.: The Pulmonary Complications of Influenza as Seen in Sheffield in 1949, Quart. J. Med. **21**:291-306 (July) 1952.

44. Minuse, E., and Davenport, F. M.: Simultaneous Recovery of Type A′ and Type C Influenza Viruses from a Patient, J. Lab. & Clin. Med. **38**:747-750 (Nov.) 1951.

45. Gutierrez, P. D.; Limson, B. M., and Sembrano, P. V.: Primary Atypical Pneumonia: A Follow-Up Study of Cases in the Phillipine General Hospital from 1947 to 1950, Acta med. philippina **8**:1-11 (July-Sept.) 1951.

46. Grist, N. R.; Landsman, J. B.; Anderson, T.; Rowan, G., and Smith, A: Studies on the Aetiology of Pneumonia in Glasgow, 1950-1951, Lancet **1**:640-646 (March 29) 1952.

47. Robertson, P. W., and Morle, K. D. F.: Explanation of "Primary Atypical Pneumonia" Syndrome, Brit. M. J. **2**:994-997 (Oct. 27) 1951.

these views and adopted a more rational one regarding the infectious nature of viral pneumonia, which they believe begins in the lower respiratory tract and spreads upward.[48] The opposite also may occur; the infection may be a descending one.

Epidemics of a viral form of pneumonia occurred in New Zealand [49] and Japan.[50] In neither place was cold agglutination of erythrocytes demonstrable. In one epidemic the symptoms included stiffness of the neck and an exanthem. Aureomycin was ineffective in therapy. The disease may have been a hitherto-undescribed systemic disease with pulmonary manifestations.

In spite of the ineffectiveness of penicillin for viral pneumonia, 87 patients were given 50,000 units every three hours during the entire febrile stage of from 5 to 10 days. Such dosage, 400,000 units daily, is much more than is needed even in the average case of pneumococcic pneumonia. It may be estimated that about 250,000,000 units of penicillin was wasted on these patients. Furthermore, there is no need for injection at such short intervals. Aureomycin given to 14 seriously sick patients was said to have shortened the disease.[51] Data so far presented regarding the use of aureomycin in the treatment of viral pneumonia reveal few, if any, adequately controlled observations. Its specific affectiveness is not yet established.[52] The same uncertainty applies to oxytetracycline and chloramphenicol.

Viral Pneumonias in Infancy.—Diffuse pneumonia with mononuclear-cell infiltration was found at necropsy in many infants over 9 days old who died suddenly.[53] It is important to differentiate the disease from accidental asphyxia or "status thymicolymphaticus." Hyperplasia of lymphoid tissue was present in the intestine, mesenteric lymph nodes, and spleen, as if some virus caused a systemic disease. It is probable that similar nonfatal disease occurs. In another study, an interstitial giant-cell pneumonia and generalized involvement of the lymphatic tissue were observed in five fatal cases.[54] Sulfonamide drugs and antibiotic agents were ineffective in therapy. The authors believe the disease to be the same as plasma-cell pneumonia or the viral pneumonia of infants. There is doubt in some investigators' minds that the presence of inclusion bodies, as reported previously by Broadhurst, by

48. Stuart-Harris, C. H.: Primary Atypical Pneumonia, Brit. M. J. **2**:1152 (Nov. 10) 1951. Wraith, D. G.: Primary Atypical Pneumonia, ibid. **2**:1403 (Dec. 8) 1951. McKendrick, G. D.: Primary Atypical Pneumonia, ibid. **2**:1403-1404 (Dec. 8) 1951. Jennings, G. H.: Clinical Features of the Pneumonias Undergoing Virus Tests, ibid. **1**:123-128 (Jan. 19) 1952.

49. West, S. R.: Epidemic of Atypical Pneumonia, New Zealand M. J. **50**:571-578 (Dec.) 1951.

50. Troen, P.: Explosive Outbreak of Atypical Pneumonia ("K-8 Fever"), A. M. A. Arch. Int. Med. **89**:258-269 (Feb.) 1952.

51. Finkel, S., and Sullivan, B. H.: Primary Atypical Pneumonia: Analysis of 123 Cases; Report of One Fatality; Review of 14 Cases Treated with Aureomycin, Dis. Chest **21**:55-69 (Jan.) 1952.

52. Tillotson, I. G., and Oseasohn, R. V.: Treatment of Primary Atypical Pneumonia—Need for Controls in Evaluation of Aureomycin Therapy, Ohio M. J. **48**:32-33 (Jan.) 1952. Finland, M.: Antimicrobial Treatment for Viral and Related Infections: I. Antibiotic Treatment of Primary Atypical Pneumonia, New England J. Med. **247**:317-325 (Aug. 28) 1952.

53. Gruenwald, P., and Jacobi, M.: Mononuclear Pneumonia in Sudden Death or Rapidly Fatal Illness in Infants, J. Pediat. **39**:650-662 (Dec.) 1951.

54. Wolman, M., and others: Studies on Interstitial Giant Cell Pneumonia: Report of 5 Cases with Autopsy, A. M. A. Am. J. Dis. Child. **83**:573-597 (May) 1952.

Adams, and by De Berardinis, is indicative of a viral infection of the respiratory tract. Similar cell inclusions were said to occur in normal infants at birth and in 31 of 32 adults.[55] The matter needs clarification.

A substance produced by a microbe, Achromobacter sp. suppressed the development of pneumonia in mice caused by the viruses of influenza and Newcastle disease.[56]

Poliomyelitis.—Several reviews of the subject bring to date recently acquired knowledge, which has caused a change in certain ideas. The disease cannot be regarded any longer as a disease chiefly of childhood, and it has been found in many regions of the world where its presence was unsuspected.[57] Melnick points out, editorially, the advances made since Enders developed a method to grow the virus by tissue culture.[58] With this technique it is possible to observe the effect of the growth of the virus on cells, to classify the different viruses, to measure the amount of specific antibody, to make serologic diagnoses of poliomyelitis, and to test the effects of possible prophylactic and therapeutic agents. By use of tissue culture, three types of poliomyelitis virus were isolated from patients in one epidemic. Expensive and cumbersome methods which require the use of monkeys no longer are needed. Passage of virus in non-nervous tissue induces a change in the characteristics of the virus, perhaps a biologic variation. Gear reviewed the knowledge of immunity to poliomyelitis.[59]

The fact that poliomyelitis virus can be cultivated in cell suspensions of dermal, muscular, and other non-neural tissue according to Faber does not mean that growth takes place in similar tissue in the body.[60] It has yet to be shown that the virus lives or causes lesions in any but nervous tissues. Jungeblut, however, found the virus in cardiac muscle in the presence of myocardial lesions suggestive of viral myocarditis.[61] Virus may be carried throughout the body by the blood stream during the earliest stages of the disease. It was detected in monkeys several days after they were fed the virus and six or seven days before the onset of paralysis.[62]

Stimson recommends treatment at home rather than in a hospital for most patients in whom poliomyelitis is suspected, for those without paralysis, and for those with slight weakness not dangerous to life.[63] To avoid the crowding of

55. Ludlam, G. B.: The Incidence and Probable Significance of Pharyngeal Inclusion Bodies, with Special Reference to Their Presence in New-Born Infants, J. Path. & Bact. **63**:687-693 (Oct.) 1951.

56. Groupé, V.; Pugh, L. H., and Levine, A. S.: Suppression of Viral Pneumonia in Mice by a Microbial Product (APM), Proc. Soc. Exper. Biol. & Med. **80**:710-714 (Aug.-Sept.) 1952.

57. Paul, J. R.: Present Concepts and Recent Advances in Acute Poliomyelitis, A. M. A. Arch. Int. Med. **90**:271-279 (Aug.) 1952.

58. Melnick, J. L.: Poliomyelitis Viruses in Tissue Culture, Editorial, Science **115**:3 (June 13) 1952.

59. Gear, J.: Immunity to Poliomyelitis, Ann. Int. Med. **37**:1-22 (July) 1952.

60. Faber, H. K.: The Question of Extraneural Growth in Vivo of Poliomyelitis Virus, Science **114**:570-571 (Nov. 30) 1951.

61. Jungeblut, C. W., and Edwards, J. E.: Isolation of Poliomyelitis Virus from the Heart in Fatal Cases, Am. J. Clin. Path. **21**:601-623 (July) 1951.

62. Horstman, D. M.: Poliomyelitis Virus in the Blood of Orally Infected Monkeys and Chimpanzees, abstracted, Federation Proc. **11**:471 (March) 1952.

63. Stimson, P. M.: Home Care of Patients with Acute Poliomyelitis, J. A. M. A. **149**:719-721 (June 21) 1952.

hospitals, unnecessary trouble, and expense, especially during an epidemic, only patients with increasing fever, urinary or respiratory difficulty, trouble in swallowing or speaking, or other signs of bulbar involvement should not be kept at home. The management of mild attacks of poliomyelitis is outlined.

According to Armstrong, the virus of poliomyelitis is disseminated better when the atmosphere is humid rather than dry.[64] The significance of this observation is not apparent, since Sabin minimizes the importance of the air-borne spread of virus from a source in the nasopharynx.[65] Infection most likely occurs by intimate contact, from food contaminated by fingers soiled with feces, or by flies. A person may spread infection as long as the virus is present in the feces.

Of 1,420 patients admitted to a hospital over a 10-year period with a diagnosis of poliomyelitis, nearly 30% did not have the disease.[66] It was mistaken for other acute infectious diseases or postinfectious states, for toxic or metabolic disorders, for vascular disease and tumors of the brain, and for other conditions.

The largest recorded epidemic of poliomyelitis in Panama occurred in 1950 to 1951.[67] The majority of patients were infants less than 2 years old.

Reports of the results of field studies on the possible immunizing effect of gamma globulin for the prevention of poliomyelitis are awaited.[68] Gamma globulin apparently is of value for the prevention of measles and has been recommended for trial to prevent the common cold, mumps, and viral hepatitis. One wonders how many more diseases it may influence.

Encephalitis.—A form of encephalitis which resembled Australian X disease of 1917-1918 caused 17 deaths among 40 patients in the Murray Valley of Australia in 1951. The virus was related serologically to Japanese B encephalitis virus. The symptoms of the disease were indistinguishable from those of other kinds of viral encephalitis. Studies are described in a series of five papers in the Jan. 26, 1952, issue of the *Medical Journal of Australia.*

In an epidemic from August to October, 1950, in Korea, about 300 American soldiers were stricken.[69] The mortality rate was 8.5%. In a follow-up study of survivors of the disease, 7% were mentally incapacitated for at least three months, and 5% had partial paralysis. Among 110 other cases of undiagnosed encephalitis, Japanese B infection was suggested as the cause by subsequent serologic tests in 65. Clinical differential is difficult.[70]

64. Armstrong, C.: Atmospheric Conditions and Spread of Poliomyelitis, Am. J. Pub. Health **41**:1231-1237 (Oct.) 1951.

65. Sabin, A. B.: Transmission of Poliomyelitis Virus: Analysis of Differing Interpretations and Concepts; Practical Implications, J. Pediat. **39**:519-531 (Nov.) 1951.

66. Dawson, K. E., and others: Acute Poliomyelitis: Differential Diagnosis of 409 Revised Diagnoses, J. Pediat. **40**:71-84 (Jan.) 1952.

67. Rodaniche, A., and Rodaniche, E. C.: An Epidemic of Acute Anterior Poliomyelitis in Panama in 1950-1951, Am. J. Trop. Med. & Hyg. **1**:784-788 (Sept.) 1952.

68. Use of Gamma Globulin in Prevention of Paralytic Poliomyelitis, Editorial, J. A. M. A. **149**:1655 (Aug. 30) 1952.

69. Lincoln, A. F., and Sivertson, S. E.: Acute Phase of Japanese B Encephalitis: Two Hundred and One Cases in American Soldiers, Korea, 1950, J. A. M. A. **150**:268-273 (Sept. 27) 1952.

70. Dickerson, R. B.; Newton, J. R., and Hansen, J. E.: Diagnosis and Immediate Prognosis of Japanese B Encephalitis: Observations Based on More Than 200 Patients with Detailed Analysis of 65 Serologically Confirmed Cases, Am. J. Med. **12**:277-288 (March) 1952.

Three neurotropic viruses were inoculated into victims of irremediable cancer. There was no effect on the neoplasms, but clinical observations from the time of inoculation could be made for the first time on diseases caused in man by any of these viruses.[71] West Nile virus caused subclinical infection in 5 of 21 inoculated patients. Ilheus virus infected 9 of 19 patients, with mild encephalitis in 3. Bunyamwera virus failed to infect three patients but caused severe encephalitis in another.

In tests using tumor implants growing in roller tube cultures, the viruses of St. Louis encephalitis and a neurotropic influenza virus were oncolytic. The viruses of Lansing poliomyelitis and Newcastle disease had no effect, and the virus of rabies seemed to stimulate the growth of the tumors.[72]

Preliminary observations suggested the identity of the viruses of epidemic keratoconjunctivitis and St. Louis encephalitis, but further work showed differences in virulence for rabbits and guinea pigs and in immunizing properties.[73] Lymphocytic choriomeningitis may cause severe disease. A case is reported in which transverse myelitis, encephalitis, and pneumonia occurred. Sulfonamide compounds and the available antibiotic agents had no effect on the disease.[74]

Rabies.—The questionable value of vaccination against rabies is discussed in two editorials.[75] The indications for and against the recommended use of vaccines now available are listed in detail. Since the disease may develop in only 10% of persons bitten by a rabid animal, it is evident that any preventive procedure used may receive undue credit for preventing a large number of infections which would not have occurred anyway. Furthermore, the danger of postvaccination paralysis in about 1 in every 500 to 1,000 vaccinated persons must be considered, although newer vaccines made on egg media are less apt to cause that sequel. A new prophylactic measure is available. Twenty-nine persons bitten by animals known to be rabid received injections of Koprowski's antiserum, and none has died of rabies. Perhaps smaller amounts and fewer injections of antirabies vaccine in combination with antiserum may prove to be most effective in preventing the disease. A physician who wishes to depart from traditionally accepted methods of prophylaxis must consider his position in court of law should a question of procedure arise. The best method of controlling rabies is elimination of the disease in animals. If dogs are the sole source of infection, mass vaccination may be satisfactory, but the problem is complicated, since almost any warm-blooded animal can transmit the disease to man.[76] During the past year rabid foxes have caused concern in eastern Pennsylvania. According to estimations in the United States, 500,000 persons annually are

71. Southam, C. M., and Moore, A.: West Nile, Ilheus and Bunyamwera Virus Infections in Man, Am. J. Trop. Med. **31**:724-741 (Nov.) 1951.

72. Pollard, M., and Bussell, R. H.: Oncolytic Effect of Viruses in Tissue Cultures, Proc. Soc. Exper. Biol. & Med. **80**:574-578 (Aug.-Sept.) 1952.

73. Ruchman, I.: Cross-Immunity Tests in Animals with Epidemic Keratoconjunctivitis and St. Louis Encephalitis Viruses, Proc. Soc. Exper. Biol. & Med. **78**:483-486 (Nov.) 1951.

74. Colmore, J. P.: Severe Infections with the Virus of Lymphocytic Choriomeningitis, J. A. M. A. **148**:1199-1201 (April 5) 1952.

75. Hammon, W. McD.: Rabies Prophylaxis, Pennsylvania M. J. **55**:335-336 (April) 1952. Prevention of Rabies, Editorial, J. A. M. A. **149**:1318-1319 (Aug. 2) 1952.

76. Koprowski, H., and Black, J.: Studies in Chick Embryo Adapted Rabies Virus: Duration of Immunity in Vaccinated Dogs, Proc. Soc. Exper. Biol. & Med. **80**:410-414 (July) 1952.

exposed to dog bite, 40,000 of whom are obliged to take antirabies prophylaxis. About 40 persons, 12,000 dogs, and 1,000 cattle die from rabies each year.[77] In Puerto Rico an epizootic occurred among mongooses.[78]

Coxsackie Viruses.—In a review of the subject, Kilbourne points out the biologic heterogenicity of a group of infectious agents whose relation to human disease remains to be determined.[79] Five years of study have merely defined the extent of the problem and suggested the association of the virus with diseases of as widely different manifestations as epidemic myalgia or pleurodynia, aseptic meningitis and herpangina. Coxsackie viruses may be present as commensals during disease caused by other agents and in healthy persons. In one study covering a 14-month period, Coxsackie viruses of seven different types were isolated from 148 fecal samples obtained from 1,232 persons. Twenty strains were isolated from the throat.[80] Evidence accumulates to indicate an etiologic relation of the viruses to herpangina and epidemic pleurodynia, or Bornholm disease.[81] Nichamin reports instances of pleurodynia associated with Coxsackie viruses in which this disease recurred several times at intervals of months or years.[82] Aureomycin was said to cause improvement in many patients. Kenyon demonstrated Coxsackie virus in the feces and oropharynx of 52 of 75 children with an epidemic disease characterized by fever, headache, nuchal and abdominal pain, and vomiting.[83] A Dutch physician reported an epidemic in which there were 358 cases of Bornholm disease associated with Coxsackie virus.[84] Pleural pain often was accompanied by a special form of tonsillitis. The circumstance suggests either that pleurodynia and herpangina occur together or that both are manifestations of the same disease. Two types of virus were isolated from one patient with herpangina.[85]

Coxsackie virus was present in over 50% of patients during an epidemic of poliomyelitis with a high ratio of paralytic and fatal cases. Antibodies for both viruses were present in two patients studied. Both viruses also were present in the intestine of persons who remained well.[86]

77. Estimated Annual Toll of Rabies, Medical News, J. A. M. A. **149**:176-177 (May 10) 1952.

78. Tierkel, E. S., and others: Mongoose Rabies in Puerto Rico, Pub. Health Rep. **67**:274-278 (March) 1952.

79. Kilbourne, E. D.: The Coxsackie Viruses and Human Disease, Am. J. M. Sc. **224**:93-102 (July) 1952.

80. Cole, R. M.; Bell, J. A.; Beeman, E. A., and Huebner, R. J.: Studies of Coxsackie Viruses: Observations on Epidemiological Aspects of Group A Viruses, Am. J. Pub. Health **41**:1342-1358 (Nov.) 1951.

81. David, J. K.; Leavitt, D., and Howitt, B. F.: Vesicular Pharyngitis: Its Relationship to Coxsackie Group of Viruses, Pediatrics **8**:672-677 (Nov.) 1951.

82. Nichamin, S. J.: Pleurodynia in Children: Clinical Observations in 54 Cases, J. A. M. A. **148**:1002-1004 (March 22) 1952.

83. Kenyon, H., and others: An Outbreak of Febrile Illness Associated with a Coxsackie Virus, Lancet **2**:153-157 (July 26) 1952.

84. Schaeffer, L. F.: Epidemic of Bornholm Disease in North Amsterdam, Nederl. tijdschr. geneesk. **95**:2938-2948 (Oct. 6) 1951.

85. Beeman, E. A.; Parrott, R. H., and Cole, R. M.: Simultaneous Occurrence of 2 Immunological Types of Group A "Coxsackie" Virus in a Case of Herpangina, Proc. Soc. Exper. Biol. & Med. **78**:295-298 (Oct.) 1951.

86. Melnick, J. L., and others: Epidemic of Paralytic Poliomyelitis Characterized by Dual Infections with Poliomyelitis and Coxsackie Viruses, J. Exper. Med. **94**:471-492 (Dec.) 1951.

Hepatitis.—Several studies reemphasize the frequency of occurrence and epidemiologic importance of viral hepatitis and viremia in patients who are not icteric. In one report, 30 instances are recorded in which there were fatigue, anorexia, abdominal pain, nausea, headache, hepatic tenderness, and a positive reaction to the thymol turbidity test and the cephalin flocculation test. Recovery was complete in four months in all but one patient, who had chronic hepatitis for a year.[87] Neefe and his associates demonstrated viremia in donors whose blood had caused the disease in recipients.[88] The donors gave no history of jaundice, were asymptomatic, and had met the criteria required by blood-collecting centers. Study revealed histologic evidence of hepatitis in three and the presence of viremia over periods of 3 to 12 months. Some test must be devised to detect carriers in order to avoid using their blood for transfusion.

In another study, nonicteric patients apparently perpetuated an epidemic of hepatitis over several years in an orphanage. Children under 3 years of age who have the disease seldom are jaundiced. They maintain a fecal carrier state for 5 to 15 months and infect other children and nurses chiefly by the fecal-oral route. No evidence of air-borne transmission was observed.[89]

Two localized outbreaks of hepatitis were studied. One was in a rural area where well water apparently was contaminated from a nearby cesspool. Twenty-two persons were infected either by drinking the water or by other contact with contaminated matter.[90] The other occurred in a military camp in which 14 cases were observed between 23 and 36 days after a cook had the disease. Contaminated food or personal contact apparently spread the infection.[91]

Efforts are in progress to establish the virus of hepatitis in experimental animals. Gledhill, Dick, and Andrewes have a virus which causes hepatitis in mice. Evidently the virus is composed of two components, neither of which is pathogenic if inoculated alone, but if injected together they cause fatal hepatitis. One component is Eperythrozoön coccoides, a Bartonella-like organism found in mice; the other resembles Cheever's JHM virus or Nelson's hepatitis virus.[92] The discovery of the dual nature of the infection in this instance should lead to a search for a similar phenomenon in other viral diseases.

Mirick and his co-workers apparently have a different filtrable agent. It was established by the inoculation of liver tissue from a patient into mice treated

87. Denber, H. C. B., and Leibowitz, S.: Acute Anicteric Virus Hepatitis: Report of 30 Cases, J. A. M. A. **149**:546-549 (June 7) 1952.

88. Neefe, J. R., and others: Demonstration of Existence of Long Term "Asymptomatic" Blood Carriers of Hepatitis Virus with Confirmation in Human Volunteers: Relationship of Carriers to Acute Viral Hepatitis in Whole Blood Recipients, abstracted, J. Clin. Invest. **31**:652 (June) 1952.

89. Capps, R. B., and Stokes, J.: Epidemiology of Infectious Hepatitis and Problems of Prevention and Control, J. A. M. A. **149**:557-561 (June 7) 1952.

90. Farquhar, J. D.; Stokes, J., and Shrack, W. D.: Epidemic of Viral Hepatitis Apparently Spread by Drinking Water and by Contact, J. A. M. A. **149**:991-993 (July 12) 1952.

91. Kaufmann, G. G.; Sborov, V. M., and Havens, W. P.: Outbreak of Infectious Hepatitis—Presumably Food-Borne, J. A. M. A. **149**:993-995 (July 12) 1952.

92. Gledhill, A. W.; Dick, G. W. A., and Andrewes, C. A.: Production of Hepatitis in Mice by the Combined Action of 2 Filtrable Agents, Lancet **2**:509-511 (Sept. 13) 1952. Niven, J. S. F., and others: Further Light on Mouse Hepatitis, ibid. **2**:1061 (Nov. 29) 1952.

previously with urethan. The virus can be transmitted serially by inoculation of extracts of organs, ascitic fluid, and blood. After an incubation period of three to four weeks, hepatitis and splenomegaly occur, and recovery is the rule. After the experiments were begun, the disease occasionally appeared in uninoculated mice, as if the infection were transmitted naturally. Antibiotics have no influence on the disease, nor is the virus neutralized by convalescent serum from patients who have had hepatitis or by gamma globulin. Gastrointestinal symptoms and abnormalities in tests of liver function occurred in volunteers inoculated with the agent.[93]

In another study, hepatitis developed after inoculation of serum from a patient with hepatitis into rats whose adrenals were suppressed by cortisone. The disease was passed to other rats by inoculation of infected rat-liver tissue. No hepatitis occurred if the serum was injected into normal rats or if cortisone-treated rats were inoculated with normal rat liver.[94]

Newcastle Disease.—An uncertainty similar to that of the relationship of Coxsackie virus to disease in man pertains to Newcastle virus. Newcastle disease of fowl is of serious import to the poultry industry, and occasionally it affects man. About 35 cases thus far have been reported, but in a number it was questionable whether the virus was not a commensal. Clearer evidence is obtained in patients known to have been exposed to the virus in laboratories. Three instances were observed in which the symptoms were malaise, photophobia, conjunctivitis, sore throat, superficial mucosal ulcers, and preauricular adenitis.[95] The disease seldom lasts more than a week; it is mild and may be inapparent. The virus was recovered from the conjunctival sac, nasal and pharyngeal washings, saliva, blood, and urine. Nelson and his co-workers report 40 new cases among 90 poultry handlers. The virus was isolated from 4 to 10 patients.[96] The virus of Newcastle disease was isolated from a patient with hemolytic anemia. The authors suggest that systemic diseases and nutritional deficiency may reduce resistance and permit the invasion of various hemotoxic viruses.[97]

Cat-Scratch Disease.—Cat-scratch disease does not always come from cats. These animals seem to be passive conveyors of infection. Infection was caused by a thorn prick, a sliver, and the handling of pork. More than 100 cases have been reported. An antigen prepared from aspirated pus and used for intradermal tests is said to be of specific diagnostic aid. The disease is indolent, is self-limited, and may last months. It may simulate any of a wide variety of neoplastic or inflammatory diseases of the regional lymph nodes. Antibiotics are ineffective in therapy except to control secondary bacterial infection. The causative virus may be related

93. Jordan, J.; Leftwich, C. I., and Mirick, G. S.: Hepatitis in Mice of Presumed Viral Origin, abstracted, J. Clin. Invest. **31**:641-642 (June) 1952.

94. Melcher, G. W.; Blunt, J. W., and Ragan, C.: Occurrence of Hepatitis in Cortisone-Treated Rats Following Inoculation with Human Infectious Hepatitis Serum, abstracted, J. Clin. Invest. **31**:649 (June) 1952.

95. Quinn, R. W., and others: Newcastle Disease in Man, abstracted, J. Clin. Invest. **31**:655 (June) 1952.

96. Nelson, C. B., and others: An Outbreak of Conjunctivitis Due to Newcastle Disease Virus (N D V) Occurring in Poultry Workers, Am. J. Pub. Health **42**:672-678 (June) 1952.

97. Moolten, S. E., and Clark, E.: Viremia in Acute Hemolytic Anemia and in Autohemagglutination: Report of a Case and Review of Literature, with Special Reference to Virus of Newcastle Disease, A. M. A. Arch. Int. Med. **89**:270-292 (Feb.) 1952.

to the psittacosis-lymphogranuloma group.[98] Mollaret and his co-workers report the discovery of the causative virus and succeeded in transmitting the disease to one of four volunteers and to monkeys. The primary lesion appeared at the site of injection 28 to 54 days after inoculation.[99]

Mumps.—An opportunity was provided to test the efficacy of mumps vaccine in susceptible Barbadian laborers imported into Florida. Of 2,825 men, 1,344 were vaccinated at the time of the first wave of an epidemic. Mumps occurred as often in the vaccinated as in the control groups during the first three weeks. It increased in a proportion of 2 to 1 after three weeks and of 3 to 1 after six weeks in the unvaccinated as compared with vaccinated men. Mumps in vaccinated men was milder, and complications were fewer.[100] Inoculation of mumps virus into the eyes of guinea pigs served as a useful method for study of changes in complement-fixing antibodies and other immunity reactions.[101]

Herpes Simplex.—A complement-fixation test is available for the diagnosis of herpes simplex. The antibody may appear by the fourth day and may persist for over 15 months. It coincides with the presence of virus-neutralizing antibody.[102]

Dengue.—Dengue virus passed through a series of mice lost its ability to induce characteristic symptoms of dengue fever in humans but evoked protective immunity against the disease and virus-neutralizing antibody. It may serve as an effective vaccine. The intradermal injection of infected mouse-brain tissue into patients with dengue causes a reaction which may serve as a diagnostic procedure.[103]

Yellow Fever.—In regard to reservoirs of infection of yellow fever in Africa, many animals were examined, but with the exception of primates, hedgehogs, and genets none so far tested seem to be important.[104]

Mononucleosis.—Among 102 students observed over a two-year period, evidence of mononucleosis was present in 51 who were not sick or had inapparent infection. Diagnosis of mononucleosis was made if two of three tests, namely, the presence of Downey cells in the blood, the heterophile antibody test, and the thymol turbidity or cephalin flocculation test, gave positive results.[105] It would seem unsafe to depend

98. Daniels, W. B., and MacMurray, F. G.: Cat-Scratch Disease: Nonbacterial Regional Lymphadenitis, A. M. A. Arch. Int. Med. **88**:736-752 (Dec.) 1951; Cat-Scratch Disease: Nonbacterial Regional Lymphadenitis; A Report of 60 Cases, Ann. Int. Med. **37**:697-713 (Oct.) 1952.

99. Mollaret, P., and others: Discovery of the Virus of Benign Inoculation Lymphoreticulosis: Experimental Inoculation to Monkey and Staining, Presse méd. **59**:701-704 (May 23) 1951.

100. Habel, K.: Vaccination of Human Beings Against Mumps: Vaccine Administered at the Start of Epidemic; Incidence and Severity of Mumps in Vaccinated and Control Groups, Am. J. Hyg. **54**:295-311 (Nov.) 1951.

101. Bolin, V., and Leymaster, G. R.: Use of Guinea Pig Eye in Study of Intraocular Infections Produced by Mumps Virus, Proc. Soc. Exper. Biol. & Med. **79**:7-12 (Jan.) 1952.

102. Gajdusek, D. C.; Robbins, M. L., and Robbins, F. C.: Diagnosis of Herpes Simplex Infections by the Complement Fixation Test, J. A. M. A. **149**:235-240 (May 17) 1952.

103. Hotta, S.: Experimental Studies on Dengue: I. Isolation, Identification and Modification of Virus, J. Infect. Dis. **90**:1-9 (Jan.-Feb.) 1952; Experimental Studies on Dengue: II. Skin Reaction Observed During Epidemic of Osaka, Japan, in 1944, ibid. **90**:10-12 (Jan.-Feb.) 1952.

104. Dick, G. W. A.: Further Studies on Susceptibility of African Wild Animals to Yellow Fever, Tr. Roy. Soc. Trop. Med. & Hyg. **46**:47-58 (Jan.) 1952.

105. Watson, J., and others: Subclinical Infectious Mononucleosis with Hepatitis: Epidemic in a Class of 102 Medical Students; a 2 Year Study, A. M. A. Arch. Int. Med. **88**:618-626 (Nov.) 1951.

on these tests for diagnosis or to assume the presence of hepatitis on the basis of the thymol turbidity test alone. Serious ocular involvement may occur during mononucleosis.[106] A case of mononucleosis presumably acquired from a transfusion of blood was reported.[107]

Epidemic Hemorrhagic Fever of the Far East.—Mayer reviews the subject historically and clinically. The disease affected American troops in Korea. Russian investigators are said to have transmitted the infection to volunteers by the inoculation of filtered blood from patients.[108]

Viral (?) Urethritis.—A publication by Graham calls attention to a widespread form of urethritis not caused by Neisseria or other bacteria in the armed forces. It affected 3% of personnel in some groups. The infection is related to coitus, has an incubation period of about 14 days, and lasts many months. Prophylaxis and treatment with penicillin are ineffective. Sulfadiazine and chloramphenicol were said to be therapeutically beneficial provided rest and abstinence from intercourse and alcohol are observed.[109] A similar form of urethritis was reported to be a common disease of young girls. Urethral dilation was said to be helpful in therapy.[110] Evidently a form of urethritis of unknown but probably of viral cause is extant.

Viral Dysentery.—As in previous autumns, I observed a mild diarrheal disease in a large percentage of students and nurses in a medical school. During the course of the low-grade epidemic, a sudden increment of more severe, febrile enteritis occurred among nurses. Although none had bloody or purulent stools, Shigella sonnei was cultivated from their stools. Evidently an epidemic of Shigella dysentery was superimposed on one of viral dysentery. The clinical course and pathologic changes in the rectal mucosa, except for degree of severity, were similar. A diagnosis is suggested by the nature of the epidemic but can be proved only by isolating Shigella in the case of shigellosis. It seemed as if a mild enteric disease might render patients more susceptible to shigellosis in the manner in which minor viral infections of the respiratory tract predispose patients to bacterial pneumonia.[111]

Gordon and his group add further support to the view that a form of dysentery may be caused by filtrable agents. Volunteers, as in previous experiments, were infected by ingesting filtrates of stools from patients with the disease. In the course of the study, two filtrable infective agents were encountered. One caused dysentery with fever; the other caused afebrile disease. Patients convalescent from infection with one virus were not immune to infection with the other.[112] Apparently there are at least two specific entities.

106. Bonynge, T. W., and Von Hagen, K. O.: Severe Optic Neuritis in Infectious Mononucleosis: Report of a Case, J. A. M. A. **148**:933-934 (March 15) 1952.

107. de Vos, J. F., and Kuipers, F. A.: A Case of Infectious Mononucleosis Transmitted Through Blood Transfusion, Nederl. tijdschr. geneesk. **95**:3036-3037 (Oct. 13) 1951.

108. Mayer, C. F.: Epidemic Hemorrhagic Fever of the Far East, or Endemic Hemorrhagic Nephroso-Nephritis: A Short Outline of the Disease, with Supplemental Data on the Results of Experimental Inoculation of Human Volunteers, Mil. Surgeon **110**:276-284 (April) 1952.

109. Graham, R. S.: Nongonococcal Urethritis, U. S. Armed Forces M. J. **3**:401-405 (March) 1952.

110. Hodges, C. V.: Chronic Urethritis in Girls, J. A. M. A. **149**:753-756 (June 21) 1952.

111. Reimann, H. A.: Viral and Bacillary Dysentery: A Dual Epidemic, J. A. M. A. **149**: 1619-1623 (Aug. 30) 1952.

112. Jordan, W. S.; Gordon, I.; Hodges, R. G., and Dorrance, W. R.: Transmission of Acute Non-Bacterial Gastroenteritis to Volunteers: Evidence for 2 Different Agents, abstracted, J. Clin. Invest. **31**:642 (June) 1952.

In experimental studies, spontaneous leukemia in mice seems to be caused by a transmissible filtrable agent. It is caused either by a virus or by the induced mutation of embryonic or postembryonic tissue cells.[113]

Studies made by electron micrography with vaccinia virus support the view that particles of virus are absorbed to cells, penetrate the cell wall, multiply, and form inclusion bodies composed of masses of elementary bodies. New generations of virus particles are released to infect other cells. Virus particles appeared to have a dense outer wall and an internal structure. Inclusion bodies usually were in contact with the nucleus of the cells.[114]

DISEASES CAUSED BY BACILLI

Shigella Dysentery.—A commission organized to study enteric infections in Korea in 1951 investigated a major epidemic of bacillary dysentery among prisoners of war. The disease probably was even more prevalent and fatal in the destitute civilian population. The authors describe the difficulties encountered in diagnosis and treatment and in control of an epidemic when hundreds of cases occurred in a short period and when medical personnel was insufficient to cope with the magnitude of the problem. The authors also remark the clinical differences between shigellosis in Asia and in the United States. Here it usually is in the form of a relatively mild transient enteritis; in Korea severe, occasionally fatal (9%), disease with bloody, purulent stools is common. The clinical differences may depend on the physical and nutritional state of the victim. It is disappointing to learn that the therapeutic and bacteriologic response of shigellosis to sulfadiazine was poor. Of 225 strains of Shigella tested, 129 were resistant to sulfonamide drugs. Satisfactory results were obtained with oxytetracycline in doses of 2 gm. initially and 1 gm. 12 and 24 hours thereafter. Aureomycin and chloramphenical also were effective.[115] Curiously, aside from a statement that "a general and high prevalence of diarrheal disease" which was not shigellosis, affected American military personnel at the same time, no mention is made of a mild, widespread enteric infection which some members of the commission regarded as viral dysentery.

According to Neter, the presence of salmonellae, shigellae, and colon bacilli in the nasopharynx may account for air-borne enteric bacillary infections in infants. He found two serotypes of Escherichia coli which probably were pathogenic. They were eliminated from the intestinal tract and oropharynx by treatment with aureomycin, oxytetracycline, or chloramphenicol.[116] Encapsulated Shigella was described

113. Gross, L.: "Spontaneous" Leukemia Developing in C3H Mice Following Inoculation in Infancy with AK-Leukemic Extracts, or AK-Embryos, Proc. Soc. Exper. Biol. & Med. **76**:27 (Jan.) 1951; Pathogenic Properties and "Vertical" Transmission of the Mouse Leukemia Agent, ibid. **78**:342 (Oct.) 1951.

114. Gaylord, W. H.; Melnick, J. L., and Bunting, H.: Intracellular Development of Vaccinia Virus, Proc. Soc. Exper. Biol. & Med. **80**:24-27 (May) 1952.

115. Hardy, A. V.; Mason, R. P., and Martin, G. A.: The Dysenteries in the Armed Forces, Am. J. Trop. Med. & Hyg. **1**:171-175 (Jan.) 1952. Hardy, A. V.: Antibiotics in the Treatment of Bacillary Dysentery, in Conference on Use of Antibiotics in Tropical Diseases, read before the New York Academy of Sciences, Section of Biology, New York, Jan. 17, 1952.

116. Neter, E.; Webb, C. R.; Shumway, C. N., and Murdock, M. R.: Study on the Etiology, Epidemiology, and Antibiotic Therapy of Infantile Diarrhea, with Particular Reference to Certain Serotypes of Escherichia Coli, Am. J. Pub. Health **41**:1490-1496 (Dec.) 1951.

for the first time. There was an antigenic relation between the capsular antigens of S. boydii 2 and that of Klebsiella Types 11 and 21.[117]

In a series of papers, McCullough and Eisele report experiments on volunteers fed cultures of Salmonella obtained from spray-dried eggs. The volunteers had previously been vaccinated against Eberthella typhosa, which may have influenced the results. Salmonella pullorum seemed to be less virulent than other varieties of Salmonella. Doses ranged from 1 and 3 billion to 10 billion bacilli. Severe but brief illness lasted two or three days, with transient bacillemia.[118] In seven cases of salmonellosis other than typhoid, chloramphenicol was reported to give beneficial results.[119]

Typhoid.—Study was made of the survivors of a typhoid epidemic which occurred 39 years ago. At the time there were 329 cases and 35 deaths. Among 146 persons whose records could be traced, the causes of death of 46 were no different from those of the general population. Of 59 persons examined, 1.7% carried E. typhosa in their enteric tract.[120]

Report was made of a patient who had three attacks of typhoid in a year. Recurrences came at intervals of 80 and 235 days. Each attack was treated with chloramphenicol. Therapy was thought to have inhibited the development of natural immunity. The second and third attacks may have been endogenous or exogenous. Several other typhoid patients treated with chloramphenicol were vaccinated subsequently to increase immunity. None had recurrences.[121] Chloramphenicol is a valuable therapeutic agent, but E. typhosa nevertheless continues to be shed in the stool for variable periods. Relapses are noted in about 20% of treated patients, and perforation or hemorrhage occur.[122] In John's experience relapse occurred in only 1 of 20 patients who received interrupted courses of chloramphenicol. Administration of the drug was stopped soon after defervescence and begun again just before a relapse was expected.[123]

Cholera.—According to Felsenfeld, strains of cholera vibrios vary in sensitivity to antibiotic agents in respect to the locality of their origin. Those from Egypt and from Bombay, Republic of India, were said to be sensitive to a variety of antibiotics;

117. Ewing, W. H.; Edwards, P. R., and Hucks, M. C.: Thermolabile Antigens of Shigella Boydii 2 Cultures with Special Reference to an Encapsulated Culture, Proc. Soc. Exper. Biol. & Med. **78**:100-105 (Oct.) 1951.

118. McCullough, N. B., and Eisele, C. W.: Experimental Human Salmonellosis: III. Pathogenicity of Strains of Salmonella Newport, Salmonella Derby, and Salmonella Barielly Obtained from Spray-Dried Whole Eggs, J. Infect. Dis. **89**:209-213 (Nov.-Dec.) 1951; Experimental Human Salmonellosis: IV. Pathogenicity of Strains of Salmonella Pullorum Obtained from Spray-Dried Whole Egg, ibid. **89**:259-269 (Nov.-Dec.) 1951.

119. Doran, J. H.: Salmonellosis: Nine Cases Successfully Treated with Chloromycetin, Ann. Int. Med. **37**:714-722 (Oct.) 1952.

120. Lieben, J.: A 39 Year Follow-Up of Typhoid Fever in Torrington, Connecticut, Connecticut M. J. **15**:983-984 (Nov.) 1951.

121. Frank, W. P.; Bower, A. G., and Chudnoff, J.: Typhoid: Report of a Case with Three Attacks in One Year, J. A. M. A. **147**:1137-1138 (Nov. 17) 1951.

122. Woodward, J. E.; Parker, R. T., and Wisseman, C. J.: Treatment of Typhoid Fever with Antibiotics, in Conference on Use of Antibiotics in Tropical Diseases, read before the New York Academy of Sciences, Section of Biology, New York, Jan. 17, 1952.

123. John, A. T., and Vinayagam, V. S.: Effect of Interrupted Courses of Chloramphenicol on Relapse-Rate in Typhoid Fever, Lancet **2**:757-759 (Oct. 18) 1952.

those from Bengal and Assam, Republic of India,[124] were resistant. In my own experience there was variation in sensitivity to amounts of 1 to 500 γ of streptomycin per cubic centimeter among vibrios from patients from one village in China.

Brucellosis.—According to Spink and his co-workers, sulfadiazine, streptomycin, aureomycin, and chloramphenicol all were successful in controlling various localized lesions of brucellosis. However, only about half the patients treated recovered promptly without a return of general symptoms. The rest had relapses or bacteremia or failed to improve. The authors suggest further trial of a combination of streptomycin and aureomycin.[125] Antibiotic therapy leaves much to be desired. A patient who had brucellosis in 1945 and 1946 was studied two years later when biopsy of the liver revealed hepatic cirrhosis as a sequel.[126]

In the second report of a national committee, the dermal sensitivity test for the diagnosis of brucellosis is condemned as useless.[127] The complement-fixation test and opsonocytophagic test are unreliable and too complicated for general use and are not recommended. A standardized Brucella antigen for the agglutination test is recommended. To be of significance the agglutination titer should be 1:320 or higher. The only proof of diagnosis is the isolation of Brucella from a patient. Methods of culture and the technic of the agglutination test are outlined.

Pertussis.—Conflicting reports concern the value of antibiotic therapy. In one study, aureomycin, chloramphenicol, and oxytetracycline each were said to cause rapid improvement in patients with pertussis. Their effects were superior to those of penicillin. Hemophilus pertussis disappeared from the oropharynx after three or four days of treatment.[128] In another study, however, the three antibiotics administered to children in similar dosage had little or no effect in reducing the incidence or severity of coughing. Oxytetracycline was more effective than the others in eliminating H. pertussis from the respiratory tract. Some potentially pathogenic bacteria of other species increased in number during therapy. Complications were greater in patients treated with aureomycin than in untreated patients. "The best treatment for pertussis is good nursing care, maintenance of adequate nutrition, hydration, and the management of complication."[129]

Diphtheria.—Polyneuritis and postdiphtheritic paralysis may be the result of an allergic response of nerve tissue to some foreign substance combined with diphtheria toxin. If that is the case, early treatment with corticotropin or cortisone may be effective.[23]

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124. Felsenfeld, O., and others: In Vitro Sensitivity of Recently Isolated Cholera Vibrios to 10 Antibiotics, Proc. Soc. Exper. Biol. & Med. **77**:287-288 (June) 1951.

125. Spink, W. W.; Hall, W. H., and Magoffin, R.: Follow-Up Study of Therapy in 48 Culturally Proved Cases of Brucellosis: Streptomycin and Sulfadiazine, Aureomycin, and Chloramphenicol (Chloromycetin), A. M. A. Arch. Int. Med. **88**:419-432 (Oct.) 1951.

126. McCullough, N. B., and Eisele, C. W.: Brucella Hepatitis Leading to Cirrhosis of the Liver, A. M. A. Arch. Int. Med. **88**:793-802 (Dec.) 1951.

127. Spink, W. W., and others: Diagnostic Criteria for Human Brucellosis: Report No. 2 of the National Research Council, Committee on Public Health Aspects of Brucellosis, J. A. M. A. **149**:805-808 (June 28) 1952.

128. Hazen, L. N., and others: Antibiotic Treatment of Pertussis: Comparison of Penicillin, Aureomycin, Chloramphenicol, and Terramycin in 150 Cases, J. Pediat. **39**:1-15 (July) 1951.

129. Weinstein, L.; Seltser, R., and Marrow, C. T.: Treatment of Pertussis with Aureomycin, Chloramphenicol, and Terramycin, J. Pediat. **39**:549-559 (Nov.) 1951.

Tetanus.—According to Puerto Rican investigators, penicillin given to patients in addition to established therapy controls secondary infection of the respiratory tract. It also eliminates tetanus bacilli, which otherwise may remain viable and elaborate more toxin. Cultures of Clostridium tetani were obtained more easily from recent localized, suppurating wounds than from extensive, chronic, deep lesions. Bacilli cultivated from wounds in 47% of patients rapidly disappeared after therapy with penicillin.[130]

Anthrax.—Haight reviewed the literature pertaining to 95 previously reported cases of meningitis caused by Bacillus anthracis and added 2 of his own. One patient received penicillin and the other aureomycin, but both died. Other antibiotics may be more effective therapeutically.[131]

Glanders.—Tulga, in Turkey, reported successful results in three patients with glanders and in experimentally infected guinea pigs after treatment with sulfadiazine. Streptomycin had no effect.[132]

Plague.—Oats treated with warfarin (3-[α-acetonylbenzyl]-4-hydroxycoumarin; Compound 42) successfully reduced the number of several species of rats in Hawaii, with the exception of the native rat, Rattus hawaiiensis. Since the native rat is important in maintaining rodent plague, some other rodenticide must be sought.[133]

Bacteroides Funduliformis.—In one hospital in a five-year period, McVay and Sprunt observed 35 cases of infection with Bacillus funduliformis, a commensal in the genitourinary and gastrointestinal tracts. Evidently disease caused by this anaerobic bacillus is more common than is believed and would be found more often if sought. It occasionally appears as fatal pneumonia or septicemia after surgical operations in areas where the bacillus resides. The clinical course is uncharacteristic, and diagnosis can be made only by isolating the bacillus from the blood. Aureomycin was said to be of therapeutic value.[134] Antibiotic therapy was employed without success in two other cases.[135]

TUBERCULOSIS

BCG Vaccine.—Conflicting reports continue to appear about the value of BCG vaccine, but most of them are favorable to its use. According to Wallgren, the results of vaccinating 17,000,000 persons suggest that the vaccine evokes specific immunity which is good enough to prevent severe tuberculosis, especially the miliary form, and meningitis. Vaccination alone will not abolish tuberculosis in a com-

130. Díaz-Rivera, R. S., and others: Management of Tetanus: Effect of Penicillin on Clostridium Tetani in Vivo, J. A. M. A. **147**:1635-1641 (Dec. 22) 1951.

131. Haight, T. H.: Anthrax Meningitis: Review of the Literature and Report of 2 Cases with Autopsies, Am. J. M. Sc. **224**:57-67 (July) 1952.

132. Effect of Streptomycin and Sulfonamides on Glanders, Foreign Letters, J. A. M. A. **149**:1051 (July 12) 1952.

133. Gross, B; Baker, R. H., and Bonnet, D. D.: Use of Warfarin-Treated Oats as a Plague Suppressive Measure in Hawaii, Pub. Health Rep. **66**:1727-1733 (Dec. 28) 1951.

134. McVay, L. V., and Sprunt, D. H.: Bacteroides Infections, Ann. Int. Med. **36**:56-76 (Jan.) 1952.

135. King, A. B.; Conklin, S. D., and Collette, T. S.: Bacteroides Infections: Report of 2 Cases Unsuccessfully Treated with Antibiotics, Ann. Int. Med. **37**:761-767 (Oct.) 1952.

munity; other older established measures are of greater importance. Vaccination is advised for newborn infants and for all other persons who still are uninfected.[136]

A 15-year study of the effect of vaccination of Amerinds with BCG was made. Among 1,551 vaccinated persons 12 died from tuberculosis; among 1,457 control subjects 65 died from the disease. The results suggest that there is a close but not absolute relationship between resistance to reinfection and hypersensitivity.[137] In another group tuberculosis developed in 21 of 22 unvaccinated children in tuberculous families, while it developed in only 2 of those who were vaccinated.[138]

Tuberculin tests made on 46 undernourished children vaccinated 6 to 24 months previously revealed no reaction in 20 and a weak response in half of the others. Several of the tuberculin-positive children had symptoms of hilitis. Under adequate nutritional and hygienic conditions the tuberculin reaction in many became stronger. The author believes that undernutrition was responsible for the untoward and poor response to vaccine.[139]

Therapy.—The successive discovery of a number of therapeutic agents keeps interest in the treatment of tuberculosis at a high level. Streptomycin was followed by paraaminosalicylic acid, later by thiosemicarbazones (amithiozone), and now by three related drugs of which isoniazid (isonicotinic acid hydrazid) seems to be the most important. The array of available agents will provide opportunity for study and evaluation over several years before conclusions can be drawn as to their relative value and disadvantages and as to whether the various agents should be used successively or in combination. The fact remains that all agents so far discovered are useful only as adjuncts to well-established methods of therapy. The matter is reviewed critically in several places.[140]

Apparently Domagk's optimistic view [141] on the therapeutic value of the isonicotinic acid group is not generally shared.[142] Isoniazid is less effective therapeutically than streptomycin, it causes toxicity at times, and tubercle bacilli rapidly acquire resistance to it. According to the report of a committee of the British Medical Association, the therapeutic effects of isoniazid are no better than those of combined therapy with streptomycin and paraaminosalicylic acid.[143] According to editorial

136. Wallgren, A.: BCG-Vaccination as Public Health Measure, Edinburgh M. J. **59**:161-177 (April) 1952.

137. Aronson, J. D., and Aronson, C. F.: Appraisal of Protective Value of BCG Vaccine, J. A. M. A. **149**:334-343 (May 24) 1952.

138. Dickie, A. W.: Tuberculosis in Families with BCG-Vaccinated and Nonvaccinated Children, Brit. M. J. **1**:632-636 (March 29) 1952.

139. Von Deschwanden, J.: Failure of BCG Vaccination, Schweiz. med. Wchnschr. **82**:283 (March 15) 1952.

140. New Antituberculosis Drugs, Editorial, J. A. M. A. **148**:1034-1035 (March 22) 1952. Caution in the Chemotherapy of Tuberculosis, Editorial, ibid. **149**:1224-1225 (July 26) 1952. Hinshaw, H. C.: Antimicrobial Therapy of Tuberculosis in 1952, Ann. Int. Med. **37**:362-366 (Aug.) 1952. Fox, H. H.: The Chemical Approach to the Control of Tuberculosis, Science **116**: 129-134 (Aug. 8) 1952.

141. Domagk, G.; Offe, H. A., and Siefken, W.: Experimental Chemotherapy of Tuberculosis (Isonicotinic Acid Hydrazide), Deutsche med. Wchnschr. **77**:573-577 (May 2) 1952.

142. Treatment of Pulmonary Tuberculosis with Isonicotinic Acid Hydrazid, Foreign Letters, J. A. M. A. **150**:49 (Sept. 6) 1952. Experiments with Isonicotinic Acid Hydrazid, Foreign Letters, ibid. **150**:50 (Sept. 6) 1952.

143. The Treatment of Pulmonary Tuberculosis with Isoniazid: An Interim Report to the Medical Research Council by Their Tuberculosis Chemotherapy Trials Committee, Brit. M. J. **2**:735-746 (Oct. 4) 1952.

comment on three papers, all published in the Nov. 1, 1952, issue of the *Lancet,* the initial attack of isoniazid on the tubercle bacillus is more powerful than that of any other agent. The drug must not be used alone. Good results were sustained only when streptomycin was added. Bacilli may resist the drug on first exposure to isoniazid.[144]

Tubercle bacilli in a patient may both gain and lose resistance to streptomycin. An instance is reported in which bacilli became highly resistant during therapy, remained so for 20 months, and disappeared when the cavity healed. Subsequently a cavity in the other lung contained streptomycin-sensitive bacilli, which disappeared after resumption of therapy.[145] Healing occurs more rapidly after surgical drainage of tuberculous abscesses if streptodornase and streptokinase are used as adjuncts to liquefy and favor the removal of thick exudate.[146] The enzymes may be harmful and should not be left in closed cavities. It was thought for a time that tuberculous meningitis was an exception to the rule and the only form of meningitis for which intrathecal therapy was needed. Lassen, however, finds intramuscular injection of streptomycin alone to give satisfactory results. Of 20 patients so treated 7 recovered. Of 12 patients with both miliary and meningeal tuberculosis only 2 recovered. None of the 50 patients mentioned had been vaccinated with BCG vaccine, and no cases of disseminated tuberculosis occurred in vaccinated persons.[147] This evidence seems to favor the use of BCG vaccine, in spite of much American opposition. It is important to differentiate tuberculous adenitis from Hodgkin's disease, because of the effectiveness of therapy in the former.[148]

Two localized epidemics of tuberculosis in schools were studied; both apparently originated in sick teachers. In England, active tuberculosis developed in nine children, and roentgenography and skin tests with tuberculin revealed the disease in three others. The "incubation" periods were between 40 and 62 days.[149] In Horton's experience tuberculosis developed in 13 of 133 pupils in a high school over a two-year period from association with a teacher with active tuberculosis.[150]

While streptomycin is of benefit in the treatment of tuberculosis of bones and joints, and its use permits operative procedures to be carried out with more safety, it must be combined with surgery to produce satisfactory results.[151]

Inoculation of the yolk sac of 5- to 8-day embryonated eggs provides a rapid method for demonstrating the presence of Myobacterium tuberculosis. The method

144. Hobby, G. L., and Lenert, T. F.: Resistance to Isonicotinic Acid Hydrazide, Am. Rev. Tuberc. **65**:771-774 (June) 1952.

145. Mitchell, R. S.; Wolinsky, E., and Steenken, W.: The Recovery of Streptomycin-Sensitive Tubercle Bacilli from a Patient with Pulmonary Tuberculosis Who Had Previously Yielded Highly Resistant Bacilli, Ann. Int. Med. **36**:1309-1317 (May) 1952.

146. Miller, J. M.; Long, P. H., and Stafford, E. S.: Clinical Experience with Streptokinase and Streptodornase in Tuberculosis, J. A. M. A. **148**:1485-1489 (April 26) 1952.

147. Lassen, H. C. A., and Neukirch, F.: On Streptomycin Therapy in Tuberculous Meningitis and Miliary Tuberculosis, Acta med. scandinav. **141**:110-124, 1951.

148. Dassen, R.; Fongi, E. G., and Gauna, E. F.: Generalized Lymph Node Tuberculosis, Prensa méd. argent. **38**:3389-3399 (Dec. 28) 1951.

149. Bevan, R. T.; Bray, P. T., and Hanly, J. F.: Outbreak of Respiratory Tuberculosis in a School, Brit. M. J. **2**:828-829 (Oct. 6) 1951.

150. Horton, R., and others: Epidemic of Tuberculosis in a High School: Report of 8 Year Follow-Up of Students Exposed, J. A. M. A. **149**:331-334 (May 24) 1952.

151. Ghormley, R. K.: Chemotherapy in Bone and Joint Tuberculosis, Editorial, J. Bone & Joint Surg. **34A**:254 (April) 1952.

is of especial value in the diagnosis of tuberculosis of the meninges and other serous surfaces. Growth occurs four to six days after inoculation.[152]

The Middlebrook-Dubos test, which once seemed to be a specific diagnostic test for tuberculosis, regrettably is unreliable. In Adcock's studies, a positive reaction occurred in 17% of serum samples from normal persons and in only 54% of those from patients with tuberculosis.[153] Bunn encountered false-positive and false-negative reactions in both human and animal serum.[154] A new test involving fixation of complement is said to be specific, and reports of its practical application are awaited.[155] In Coldwell and Pitner's experience, none of the tests thus far proposed is sufficiently specific to be useful in the diagnosis of tuberculosis.[156]

According to Lurie, the greater part of the lungs of susceptible rabbits is involved after experimental infection. In resistant animals, bacilli multiply only a short time and are rapidly destroyed. Whatever causes the destruction of bacilli results in the rapid development of allergic sensitiveness and of antibodies, as if these factors were merely the result of the infection. If so, they are of less importance than genetic factors in resistance to infection.[157] These views have a bearing on the controversy as to whether hypersensitivity to tubercle bacilli is beneficial or harmful in resistance to tuberculosis, especially in relation to vaccination with BCG.

Friou concluded that the negative reaction to tuberculin commonly found in sarcoid disease does not support a theory of relationship of sarcoidosis to tuberculosis. During sarcoidosis the skin reacts less strongly or not at all to other antigens as well. The suppression of reaction is an unspecific phenomenon.[158]

DISEASES CAUSED BY COCCI

Meningitis.—Therapy of bacterial meningitis still is imperfect. Because in one group of 43 patients with pneumococcic meningitis 13 (30%) died after treatment with penicillin, as compared with 11 (79%) of 14 treated with penicillin and aureomycin combined, it seemed that therapeutic antagonism might have been responsible.[159] Even if antagonism played no role, antibiotics should be used

152. Brueck, J. W., and Buddingh, G. J.: Isolation of M. Tuberculosis by Inoculation of the Yolk Sac of Embryonated Eggs, Proc. Soc. Exper. Biol. & Med. **80**:589-591 (Aug.-Sept.) 1952.

153. Adcock, J.; Haley, R. R., and Davey, W. N.: The Middlebrook Hemagglutination Test for Tuberculosis: An Evaluation in Normal Subjects and in Patients with Tuberculosis, J. Lab. & Clin. Med. **38**:736-741 (Nov.) 1951.

154. Bunn, P., and others: Some Observations upon the Middlebrook-Dubos Hemagglutination Test in Man and Animals, Ann. Int. Med. **37**:84-95 (July) 1952.

155. Maillard, E. R., and Gagliardo, F. J.: New Serologic Test for Tuberculosis: Preliminary Report, Am. Rev. Tuberc. **64**:675-678 (Dec.) 1951.

156. Colwell, C. A., and Pitner, G.: Agglutination of Sensitized Sheep Erythrocytes and Collodion Particles by Tuberculous and Normal Sera, J. Clin. Invest. **31**:238-244 (Feb.) 1952.

157. Lurie, M. B.; Abramson, S., and Heppleston, A. G.: On Response of Genetically Resistant and Susceptible Rabbits to Quantitative Inhalation of Human Type Tubercle Bacilli and Nature of Resistance to Tuberculosis, J. Exper. Med. **95**:119-134 (Feb.) 1952.

158. Friou, G. J.: Delayed Cutaneous Hypersensitivity in Sarcoidosis, abstracted, J. Clin. Invest. **31**:630 (June) 1952.

159. Lepper, M. H., and Dowling, H. F.: Treatment of Pneumococcic Meningitis with Penicillin Compared with Penicillin Plus Aureomycin: Studies Including Observations on Apparent Antagonism Between Penicillin and Aureomycin, A. M. A. Arch. Int. Med. **88**:489-494 (Oct.) 1951.

separately. Intrathecal therapy is not necessary. According to Feibush and his associates, optimism is too great about the success in treating pneumococcic meningitis. They report a mortality rate of 70% among 22 adult patients apparently adequately treated with combined penicillin and sulfonamides. They believe that poor nutrition and complicating diseases were partly responsible. Massive injections of 1,000,000 units of penicillin every two hours given intramuscularly, with sulfadiazine, are recommended.[160]

Of 30 children between the ages of 3 and 51 months with meningitis caused by Hemophilus influenza Type B, 18 were treated with aureomycin and sulfadiazine and 12 with chloramphenicol. Of the 18, 3 died, and all treated with chloramphenicol recovered.[161] Two cases of meningitis in newborn infants were caused by Listerella monocytogenes. One infant died; the other, to whom aureomycin and penicillin were given, recovered.[162]

Cerebrospinal meningitis seems to be the most widespread epidemic disease in Africa. Outbreaks occur in hot dry weather; yet, according to a report, natives are particularly affected because they huddle together to keep warm in winter. Carriers are common, and when the carrier rate exceeds 50% an epidemic is imminent.[163] According to Waddy, absolute humidity is of importance in the spread of air-borne diseases, particularly those of the respiratory tract. Dryness of the atmosphere may lower the resistance to infection of the nasopharyngeal mucosa and account for epidemics of lobar pneumonia and smallpox in the Sahara. The same situation may apply in epidemics of influenza in the temperate zones.[164] Editorial comment emphasizes the complexity of this subject.[165]

Rheumatic Fever.—Important studies were made on the influence of hormonal therapy in the treatment of rheumatic fever and on the prevention of rheumatic fever with antibiotic prophylaxis. Eighteen patients with severe rheumatic carditis were treated with corticotropin and cortisone by Kuttner and her co-workers. Clinical improvement occurred in all and was most striking in those acutely sick. Carditis subsided in some but not in all, even after three courses of therapy. Of 12 patients treated during their first rheumatic attack, all had cardiac murmurs and 11 had cardiomegaly. In other patients active carditis persisted for weeks. It was not clear whether hormonal therapy significantly decreased the duration of carditis or influenced the degree of cardiac injury.[166]

Preliminary report of observations by Hauser indicates no superiority of corticotropin over salicylate therapy in rheumatic fever in adults. After a six-month period,

160. Feibush, J. S.; Murphy, E. J., and Lubart, A.: Pneumococcal Meningitis in Adults, Ann. Int. Med. **37**:65-74 (July) 1952.

161. Schoenbach, E. B.; Spencer, H. C., and Monnier, J.: Treatment of H. Influenzae Meningitis with Aureomycin and Chloramphenicol: Experience in 30 Consecutive Cases, Am. J. Med. **12**:263-276 (March) 1952.

162. Line, F. G., and Cherry, W. B.: Meningitis Due to Listerella Monocytogenes, J. A. M. A. **148**:366-369 (Feb. 2) 1952.

163. Cerebrospinal Meningitis in Africa, Medical News, J. A. M. A. **149**:176-177 (May 10) 1952.

164. Waddy, B. B.: Climate and Respiratory Infections, Lancet **2**:674-677 (Oct. 4) 1952.

165. Humidity and Infection, Lancet **2**:668-669 (Oct. 4) 1952.

166. Kuttner, A. G., and others: Effect of ACTH and Cortisone on Rheumatic Carditis: Observations on 18 Cases, J. A. M. A. **148**:628-634 (Feb. 23) 1952.

there was no significant difference in initial response or in the incidence of persistent cardiac murmurs.[167] According to Hansen administration of cortisone or corticotropin does not seem to justify change in the over-all treatment of children with rheumatic fever. Recurrent attacks are likely to occur.[168] A similar view is expressed by English observers.[169]

The course of 1,000 patients who had had rheumatic fever was followed for 20 years by Bland and Jones. Of 653 who had signs of heart disease in the initial attack, no evidence of cardiac involvement remained in 108 (16%). Of the 347 without early known heart disease, valvular defects occurred later in 154 (14%). At the end of the first decade 202 had died; at the end of the second decade 301 were dead, most from rheumatic fever and cardiac failure and 10% from bacterial endocarditis. Recurrences of rheumatic fever in subsequent five-year periods occurred in 20, 10, 5, and less than 5%, respectively. Among 699 survivors, only 1 of 4 had cardiac disorder.[170]

Prevention.—Two procedures now are available for the prevention of attacks of rheumatic fever. The initial streptococcic infection may be prevented by the continuous administration of sulfadiazine or penicillin, or the streptococcic infection itself may be treated with one of the antibiotic agents. Sulfonamide therapy is ineffective. Official opinion avers that "all patients who have recently had an attack of rheumatic fever with associated signs of carditis should receive one of these two drugs (penicillin or sulfadiazine) for a minimum period of two years.[171]

There are, however, theoretic objections to the practice of giving sulfadiazine or penicillin for the prevention and treatment of sore throat due to hemolytic streptococci. One is the ever-present possibility of sensitization to the drugs; another concerns the rapid elimination of streptococci from the throat, which interferes with the formation of natural antibodies in the form of antibacterial immunity and hypersensitivity. In experiments in mice, acquired resistance to infection with streptococci was inversely proportional to the efficacy of treatment with penicillin and the rapid elimination of the streptococci.[172]

Another important reason for not applying prophylactic or therapeutic measures to all persons with sore throat rests on the observation that hemolytic streptococci are the cause in only about 25% of cases of acute pharyngitis.[85] Less than 2% of all minor infections of the respiratory tract are streptococcic in origin.

In attempts to determine the relation between streptococci and rheumatic fever, English investigators prepared a vaccine from Group A hemolytic streptococci in the presence of chondroitin sulfate. Rabbits vaccinated with this product showed

167. The Use of Salicylate in Rheumatic Fever, Bull. Rheum. Dis. **2**:9 (Jan.) 1952.

168. Hanson, A. E.: Importance of Early Diagnosis in Acute Rheumatic Fever, J. A. M. A. **148**:1481-1485 (April 26) 1952.

169. Bywaters, E. G. L., and Dixon, A. St. J.: The Effect of Corticotropin in Rheumatic Fever, Quart. J. Med. **21**:307-326 (July) 1952.

170. Bland, E. F., and Jones, T. Duckett: Rheumatic Fever and Rheumatic Heart Disease: A 20 Year Report on 1,000 Patients Followed Since Childhood, Circulation **4**:836-842 (Dec.) 1951.

171. Rammelkamp, C. H.: Prevention of Rheumatic Fever, Bull. Rheumat. Dis. **2**:13-14 (March) 1952.

172. Speck, R. R., and Jawetz, E.: Effect of Antibiotics on Development of Resistance to Hemolytic Streptococcus Infection, Proc. Soc. Exper. Biol. & Med. **79**:510-512 (March) 1952.

changes in the joints as compared with controls. Evidently streptococci may provide the hapten which converts tissue protein into autoantigens with a new specificity, instead of the reverse process taking place.[173]

Apparently antibodies specific for types of Group A streptococci play a role in immunity. While Type 14 streptococci were present in about a half of 43 men, infection was observed in 7 whose blood contained no specific antibody, in contrast to absence of infection in those who possessed antibodies.[174]

At the May meeting of the Association of American Physicians, Rammelkamp contrasted the epidemiologic behavior of acute nephritis and rheumatic fever in regard to previous infection of the respiratory tract with Group A streptococci. Acute nephritis followed streptococcic sore throat in 0.08 to 3% of cases, while rheumatic fever developed in 3% of all patients. Most instances of nephritis occurred after infection with Type 12 streptococci, as if this type were especially implicated in the cause of nephritis.

In a follow-up study of the ultimate outcome of acute nephritis in childhood, the records of 27 patients who had had an attack over 20 years ago were studied. One had died. The ages of the others ranged from 26 to 44 years. None had urinary abnormalities, and the blood pressure was normal in 22. Apparently acute nephritis in childhood is rarely an initiating factor of chronic nephritis.[175]

Basing their diagnosis on electrocardiographic evidence, tachycardia, or transient murmurs, European physicians report "myocarditis" in about 4% of 3,000 cases of scarlet fever and 4.5% of 800 cases of tonsillitis. The incidence was high in adults. Evidence of myocardial involvement usually appeared in the first week and lasted several weeks. No serious consequences were detected.[176]

For a time after the introduction and use of adrenocortical hormones for patients with rheumatoid arthritis, it was thought that the disease, after all, might not be infectious but might be caused by hormonal influences. Evidently, the infectious theory is revived. Nava suggests that any one of a number of bacteria may be the incitant and that the disease is continued by sensitization and hyperreaction of the patient to substances in his own tissues.[177]

Endocarditis.—Despite careful management and antibiotic therapy, the mortality rate for subacute bacterial endocarditis hovers between 20 and 30%. A fatal case is described in which a patient was treated late in the first episode and for several recurrences within a year. Apparently adequate antibiotic treatment failed to

173. Glynn, L. E., and Holborow, E. J.: Conversion of Tissue Polysaccharides to Auto-Antigens by Group-A Beta-Haemolytic Streptococci, Lancet **2**:449-451 (Sept. 6) 1952.

174. Wannamaker, L. W., and Denny, F. W.: Demonstration in Man of Type Specific Immunity to Streptococcal Infections, abstracted, J. Clin. Invest. **31**:669 (June) 1952.

175. Hebert, H. J.: Acute Glomerulonephritis in Childhood: Study of Late Prognosis of 27 Cases, J. Pediat. **40**:549-557 (May) 1952.

176. Bengtsson, E.; Birke, G., and Wingstrand, H.: Acute Non-Specific Myocarditis in Scarlet Fever and Acute Haemolytic Tonsillitis: Clinical Investigation of 3,069 Cases of Scarlet Fever, 798 Cases of Acute Tonsillitis, and 333 Cases of Haemolytic Streptococcus Carriers, Cardiologia **18**:360-376, 1951.

177. Nava, P.: On the Possible Role of Sensitization by Homologous Tissue Products in Rheumatoid Arthritis: Preliminary Note, Brasil-méd. **65**:464-466 (Nov. 3, and 10) 1951.

eliminate streptococci, which were found in valvular lesions at necropsy.[178] In another instance, cure is reported after therapy with 86,000,000 units of penicillin daily.[179]

Although the usual length of time recommended for treatment is four to eight weeks, two investigators shortened the time to two weeks but gave 2,500,000 units of crystalline penicillin intramuscularly every four hours. Results as good as those in patients treated longer were obtained.[180] Aureomycin was given to eight patients, and two were said to be cured. Several of the others were subsequently treated with penicillin and recovered. Since aureomycin is not bactericidal, relapse was common. Aureomycin is less effective than penicillin and is needed only as an adjunct to penicillin when penicillin is ineffective or when Gram-negative bacteria are the cause.[181]

It is shocking to read that competent clinicians still recommend splenectomy for the treatment of subacute bacterial endocarditis. Several splenectomized victims were said to have recovered, but they also received antibiotic therapy.[182] Splenectomy for the treatment of endocarditis was condemned a decade ago by Lord Horder and others at a meeting of the Association of American Physicians.

In experimental studies, rats subjected to low barometric pressure over long periods, in contrast with rats kept under average conditions, acquired endocarditis after inoculation with streptococci. They may serve as convenient test subjects for further study of subacute bacterial endocarditis.[183] Certain strains of viridans streptococci trained to resist a variety of antibiotic agents acquired characteristics which were identical with those of enterococci, as if mutation had occurred.[184]

Rosenow continues to publish fantastic ideas about streptococci. He now believes that a specific neurotropic Streptococcus may participate in causing criminal tendencies in persons so inclined. Changes in the cutaneous reactions to streptococci observed in inmates of a prison may determine whether parole is warranted.[185]

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178. Bader, M.; Bader, R., and Friedberg, C. K.: Causes of Failure in Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **148**:1498-1501 (April 26) 1952.

179. Whipple, R. L.: Cure of Patient with Very Resistant Streptococcus Viridans Endocarditis with Massive Penicillin Therapy (Average Daily Dose of 86 Million Units), Am. Heart J. **42**:414-420 (Sept.) 1951.

180. Hamburger, M., and Stein, L.: Streptococcus Viridans Subacute Bacterial Endocarditis: Two Week Treatment Schedule with Penicillin, J. A. M. A. **149**:542-545 (June 7) 1952.

181. Friedberg, C. K.: Treatment of Subacute Bacterial Endocarditis with Aureomycin, J. A. M. A. **148**:98-102 (Jan. 12) 1952.

182. Fellinger, K., and Weissel, W.: Splenectomy in Therapy of Subacute Bacterial Endocarditis, Deutsche med. Wchnschr. **77**:499-500 (April 18) 1952.

183. Highman, B., and Altland, P. D.: Experimental Bacterial Endocarditis in Altitude Rats: Shortening Acclimatization Period, Proc. Soc. Exper. Biol. & Med. **78**:590-593 (Nov.) 1951.

184. Feltz, M., and Clapper, W. E.: Antigenic Similarity of Some Trained Resistant Strains of Viridans Streptococci to Streptococcus Fecalis, Proc. Soc. Exper. Biol. & Med. **78**:491-492 (Nov.) 1951.

185. Rosenow, E. C., and Rosenow, O. F.: Influence of Streptococcal Infections on the Compulsive Behavior of Criminals, Postgrad. Med. **10**:423-432 (Nov.) 1951.

OTHER DISEASES

Histoplasmosis.—During the second World War, two small epidemics of an unusual kind of pneumonia thought to be viral affected groups of soldiers who had occupied underground places. It was called cave sickness and Camp Gruber pneumonia. The cause was not discovered. Seven years later studies revealed Histoplasma capsulatum in the earth of a cellar where one group of soldiers had been quartered. Of the 26 victims who had been there, 22 were traced and studied in 1951. All reacted to the histoplasmin skin test, in four the complement fixation test gave a positive result, and disseminated areas of calcification were present in the lungs of 16.[186] One of the cases was reported separately.[187] The epidemic evidently had been one of unrecognized histoplasmosis. Retrospective inquiry into other similar outbreaks likewise may reveal their cause.

Although histoplasmosis first was encountered by Darling in three patients in Panama 45 years ago, it received little attention there until recently. By a curious coincidence, the same case was described as the fourth one recognized in Panama in different issues of a journal by two groups of authors.[188] The patient was a child of 3 months, said to be the youngest victim on record and possibly was infected in utero. Because of the occasional discovery of nontuberculous pulmonary calcification and the number of persons whose skin reacts to histoplasmin, many cases probably are unrecognized in Panama. Tucker refers to two cases in Cuba,[188b] but despite Suarez' demonstration of histoplasmin reactors in Puerto Rico, no cases have been discovered there.

Only 10 of 417 French children reacted to the histoplasmin skin test. Even the positive reactions were suspected of being nonspecific.[189] The highest incidence of histoplasmin sensitivity in persons is in eastern-central United States. Elsewhere the percentage of reactors is low. Except for unpublished observations of Rizk in Lebanon, where the incidence of reactors was nil, almost nothing is known of the problem in Asia. A few cases were recognized in South Africa, three in Java, and isolated ones in Europe.[190]

Climatic variations may play an important role in the prevalence and spread of histoplasmosis. According to Furcolow and Sitterley, persons in Kansas whose skin reacts to histoplasmosis are far more common (84%) in humid areas than in dry regions (1 %).[191] Apparently, in contrast with Coccidioides immitis, moisture favors H. capsulatum. In a highly endemic area, specimens for marrow biopsy were

186. Furcolow, M., and Larsh, H. W.: Direct Isolation of Histoplasma Capsulatum from Soil: Probable Etiological Relationship to Camp Gruber Pneumonitis, Proc. Soc. Exper. Biol. & Med. **80**:246-248 (June) 1952.

187. Schwartz, B., and Spitz, L. J.: Histoplasmosis in Epidemic Form: Follow-Up Study, A. M. A. Arch. Int. Med. **89**:541-546 (April) 1952.

188. (*a*) Draheim, J. H.; Mitchell, J. R., and Elton, N.: Histoplasmosis: Fourth Case Report from the Canal Zone, Am. J. Trop. Med. **31**:753-760 (Nov.) 1951. (*b*) Tucker, H. A.: Histoplasmosis on the Isthmus of Panama: Summary of Epidemiologic Survey (1949-1950) and Report of Fourth Local Case (1951), Am. J. Trop. Med. & Hyg. **1**:462-469 (May) 1952.

189. Fréour, P., and Arnoux-Laujac: Note on 400 Cutaneous Histoplasmin Tests Performed in Children, J. franc. méd. et chir. thorac. **5**:576-580, 1951.

190. Mochi, A., and Edwards, P. Q.: Geographical Distribution of Histoplasmosis and Histoplasmin Sensitivity, Bull. World Health Organ. **5**:259-291, 1952.

191. Furcolow, M. L., and Sitterley, J.: Further Studies of Geography of Histoplasmin Sensitivity in Kansas and Missouri, J. Kansas M. Soc. **52**:584-588 (Dec.) 1951.

obtained from 193 patients with symptoms suggestive of histoplasmosis. Apparently the procedure is of little diagnostic value; H. capsulatum was found only once.[192] In an endemic area in Kentucky, H. capsulatum was not found in any of 1,307 appendixes removed at operation.[193] This is in contrast to a prior observation of another investigator, who reported H. capsulatum in 12% of appendixes, basing his finding on morphologic grounds alone,[194] as was critically discussed in last year's review. Pinkerton and Iverson describe three cases in which histoplasmosis was mistaken for sarcoidosis until H. capsulatum was discovered in the tissue.[195] Histoplasmosis may, at times, cause disease indistinguishable from sarcoidosis. Histoplasma-like bodies were found in the splenic cells of normal horses in tissue-culture preparations.[196]

A case of disseminated coccidioidomycosis occurred in a patient in Rhode Island who had served in the Armed Forces in southern California about five years previously.[197] Meningitis is a serious feature of coccidioidomycosis. It may occur promptly after the primary infection or two or three years later, and it may last several years, usually ending fatally. Antibiotic therapy is ineffective.[198]

Therapeutic success is reported in isolated instances of mycotic infections. Because of the apparent good results in the treatment of blastomycosis with "stilbamidine,"[199] the drug was administered to a patient with actinomycosis; results were equally good.[200] In another instance, actinomycotic empyema caused by Actinomyces israeli seemed to be cured after a total of 213 gm. of chloramphenicol was given over 64 days.[201] Cryptococcosis was said to be favorably influenced by treatment with cyclohexamine (acti-dione®).[202]

Geotrichum was isolated from the blood of two patients, one an infant with tuberculosis and the other a diabetic patient aged 79. Evidently in rare instances this fungus, like others, may become invasive in debilitated persons.[203]

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192. Schwartz, S. O., and Barsky, S.: Report of 193 Marrow Biopsy Specimens Cultured for Histoplasma Capsulatum, Blood **7**:545-549 (May) 1952.

193. Christopherson, W. M.; Miller, M. P., and Kotcher, E.: Examination of Human Appendixes for Histoplasma Capsulatum, J. A. M. A. **149**:1648-1649 (Aug. 30) 1952.

194. Raftery, A.: Subclinical Histoplasmosis: Gastrointestinal Histoplasmosis of Children, J. A. M. A. **145**:216-219 (Jan. 27) 1951.

195. Pinkerton, H., and Iverson, L.: Histoplasmosis: Three Fatal Cases with Disseminated Sarcoid-Like Lesions, A. M. A. Arch. Int. Med. **90**:456-467 (Oct.) 1952.

196. Randall, C. C.; Orr, M. F., and Schell, F. G.: Detection by Tissue Culture of an Organism Resembling Histoplasma Capsulatum in an Apparently Healthy Horse, Proc. Soc. Exper. Biol. & Med. **78**:447-450 (Nov.) 1951.

197. Falkinburg, L. W.: Disseminated Coccidioidomycosis: Report of a Case in the New England Area, J. A. M. A. **150**:216-217 (Sept. 20) 1952.

198. Jenkins, V. E., and Postlewaite, J. C.: Coccidioidal Meningitis: Report of 4 Cases with Necropsy Findings in 3 Cases, Ann. Int. Med. **35**:1068-1084 (Nov.) 1951.

199. Schoenbach, E. B.; Miller, J. M., and Long, P. H.: The Treatment of Systemic Blastomycosis with Stilbamidine, Ann. Int. Med. **37**:31-45 (July) 1952.

200. Miller, J. M.; Long, P. H., and Schoenbach, E. B.: Successful Treatment of Actinomycosis with "Stilbamidine," J. A. M. A. **150**:35 (Sept. 6) 1952.

201. Littman, M. L.; Paul, J. S., and Fusillo, M. H.: Treatment of Pulmonary Actinomycosis with Chloramphenicol: Report of a Case, J. A. M. A. **148**:608-612 (Feb. 23) 1952.

202. Carton, C. A.: Treatment of Central Nervous System Cryptococcosis: A Review and Report of 4 Cases Treated with Actidione, Ann. Int. Med. **37**:123-145 (July) 1952.

203. Bendove, R. A., and Ashe, B. I.: Geotrichum Septicemia, A. M. A. Arch. Int. Med. **89**:107-110 (Jan.) 1952. Kaliski, S. R.; Beene, M. L., and Mattman, L.: Geotrichum in Blood Stream of an Infant, J. A. M. A. **148**:1207-1209 (April 5) 1952.

Typhus Fever.—Since the perpetuation of the rickettsiae of murine typhus fever depends on the frequency of contacts of rats and fleas, knowledge of their relationship is important. Studies in Texas reveal the constant presence of ectoparasites on rats. An increase in the number of human victims of murine typhus lags about two months behind the seasonal increase in the abundance of fleas on rats.[204] According to experience in Korea, application of DDT powder among military personnel resulted in an increase of infestation with lice. Tests revealed that local selective breeding results in the development of body lice resistant to DDT.[205]

Brill's disease was diagnosed in 26 patients in Yugoslavia, where typhus is endemic and was epidemic from 1942 to 1945.[206] Mild recrudescences in persons who had had typhus years before support Zinsser's theory that man is an interepidemic reservoir of louse-borne typhus.

As predicted after its discovery was announced, rickettsialpox is not limited to New York City and its environs. Cases of it have been observed in Boston, Philadelphia, and now in West Hartford, Conn., among residents of an apartment house.[207] Many mice on the premises were found to be carriers of Rickettsia akari.[208]

Q Fever.—German observers report two unusual cases of Q fever, one with a maculopapular exanthem and the other with three recurrences over a three-month period. Oxytetracycline was said to have caused rapid improvement in both patients.[209] According to Italian investigators, geese, ducks, and pigeons can be infected with Coxiella burneti and may be added to list of possible sources of the disease for man.[210] Agglutinating and complement-fixing antibodies persist in the blood for many months after recovery from Q fever. Their presence in a single test in the absence of clinical or other evidence is of no diagnostic value.[211]

Psittacosis.—An agent of the psittacosis-ornithosis group was isolated from egrets in Louisiana. It resembles the pneumonitis virus previously isolated during a localized epidemic of pneumonia in Louisiana.[212] Wild birds may have been the source of infection. A number of isolated cases of psittacosis were observed in

204. Davis, D. E.: Observations on Rat Ectoparasites and Typhus Fever in San Antonio, Texas, Pub. Health Rep. **66**:1717-1726 (Dec. 28) 1951.

205. DDT Resistant Body Lice, Editorial, J. A. M. A. **148**:941 (March 15) 1952.

206. Murray, E. S., and others: Brill's Disease: Study of 26 Cases in Yugoslavia, Am. J. Pub. Health **41**:1359-1369 (Nov., Pt. 1) 1951.

207. Rickettsialpox, Medical News, J. A. M. A. **148**:656 (Feb. 23) 1952.

208. Eustis, E. B., and Fuller, H. S.: Rickettsialpox: Recovery of Rickettsia Akari from Mites, Allodermanyssus Sanguineus, from West Hartford, Conn., Proc. Soc. Exper. Biol. & Med. **80**:546-549 (July) 1952.

209. Simrock, W., and Siegert, R.: Two Rare Cases of Q Fever, Deutsches Arch. klin. Med. **198**:578-587, 1951.

210. Babudieri, B., and Moscovici, C.: Experimental and Natural Coxiella Burneti Infection in Birds, Rendic. Ist. super. san. **15**:215-219, 1952.

211. Lennette, E. H., and others: Q Fever Studies: Development and Persistance in Man of Complement-Fixing and Agglutination Antibodies to Coxiella Burnetii, J. Immunol. **68**:591-598 (May) 1952.

212. Rubin, H.; Kissling, R. E.; Chamberlain, R. W., and Eidson, M. E.: Isolation of Psittacosis-Like Agent from the Blood of Snowy Egrets, Proc. Soc. Exper. Biol. & Med. **78**:696-697 (Dec.) 1951.

association with parakeets after the quarantine on them was raised in several localities.[213] Pheasants may be added to the list of avian sources of ornithosis.[214]

A newly recognized member of the Myagawanella group may be an agent which causes a form of pneumonia in sheep.[215]

Leptospirosis.—A review of the literature of leptospirosis and a discussion of new cases were published by Gsell in Switzerland.[216] An outbreak of encephalitis among American military personnel on Okinawa Island was regarded as of viral origin. Years afterward, because of a history of immersion of the men in polluted water and conjunctival irritation noted on the records, leptospirosis was suspected, although none of the victims had been jaundiced. Some of them were traced, and the presence in their blood of agglutinin for Leptospira hebdomidis B supported the retrospective diagnosis.[217] A similar follow-up study was made in the United States on 536 samples of blood taken from persons who had had nonbacterial meningitis of unknown cause. Serologic tests revealed agglutinin for Leptospira in a titer of probable significance in 24.[218] Evidently leptospiral meningitis is mistaken at times for meningitis caused by the viruses of mumps, lymphocytic choriomeningitis, poliomyelitis, and other diseases. Evidence suggests also that a disease known during the second World War as Fort Bragg fever, supposedly viral in origin, is caused by an unidentified Leptospira. The serum of patients and of inoculated animals contains an antigen specific for Leptospira autumnalis.[219]

Amebiasis.—Extraintestinal amebiasis is discussed in two papers. In one study, hepatic involvement was found in 6 of 28 patients with amebiasis. Amebic hepatitis is more common than amebic abscess. Diagnosis is suggested by an enlarged tender liver, a peculiar pigmentation of the skin resembling sun tan, elevation of the right leaf of the diaphragm, evidence of slight hepatic dysfunction in appropriate tests, the reaction to the complement-fixation test, and the response to therapy with amebacidal agents. Chloroquine is the drug of choice for hepatic disease, with diiodohydroxyquinoline (diodoquin®) in addition if intestinal amebiasis also is present.[220] In the other study, pulmonary lesions were demonstrated in 16 of 170 cases of amebiasis. Atelectasis, amebic pneumonia, and abscess may occur. In cases of involvement of the right lower lobe of the lung of obscure cause, amebiasis should be considered in diagnosis, especially in regions where the disease is endemic.[221]

213. Outbreaks of Psittacosis, Medical News, J. A. M. A. **148**:1135 (March 29) 1952.

214. Ward, C. G., and Birge, J.: Psittacosis (Ornithosis) Following Contact with Pheasants: Report of a Case, J. A. M. A. **150**:217-219 (Sept. 20) 1952.

215. McKercher, D. G.: A Virus Possibly Related to the Psittacosis-Lymphogranuloma-Pneumonitis Group Causing a Pneumonia in Sheep, Science **115**:543-544 (May 16) 1952.

216. Gsell, O.: Leptospirosis: Clinical Features and Epidemiology of Weil's Disease, Field, Harvest and Swamp-Fever, Swineherds' Disease, Canicola Fever, Ricefield Fever, and Other Human and Animal Infections Due to Leptospira, Bern, Hans Huber, 1952, pp. 1-323.

217. Gauld, R. L., and others: Leptospiral Meningitis: Report of Outbreak Among American Troops on Okinawa, J. A. M. A. **149**:228-231 (May 17) 1952.

218. Beeson, P. B., and Hankey, D. D.: Leptospiral Meningitis, A. M. A. Arch. Int. Med. **89**:575-583 (April) 1952.

219. Gochenour, W. S., and others: Leptospiral Etiology of Fort Bragg Fever, abstracted, Federation Proc. **11**:469 (March) 1952.

220. Zavala, D. C., and Hamilton, H. E.: The Recognition and Treatment of Hepatic Amebiasis, Ann. Int. Med. **36**:110-125 (Jan.) 1952.

221. Schorr, S., and Schwartz, A.: The Roentgenologic Manifestations of Amebiasis of the Liver with Concomitant Findings in the Chest, Am. J. Roentgenol. **66**:546-554 (Oct.) 1951.

Tests in a large institution for mentally deficient persons revealed that the administration prophylactically of a combination of bismuth glycolylarsanilate (milibis®) and chloroquine phosphate (aralen phosphate®) over seven days was effective in eliminating cysts of Ameba histolytica in 93% of inmates. The same therapy also protects against infection with malaria.[222]

A number of important papers appear in the commemorative issue of the *Journal of Tropical Medicine and Hygiene* of Jan., 1952, in honor of Charles Franklin Craig. Faust outlines the modern criteria for the laboratory diagnosis of amebiasis. According to D'Antoni, amebiasis is underestimated as to incidence, overestimated as to lethal possibilities, and largely mismanaged from the standpoint of public health. Its clinical manifestations "are typically atypical," and no entirely satisfactory amebacidal drug is available at present.

Malaria.—In the Craig commemorative issue of the *Journal of Tropical Medicine and Hygiene,* Russell discusses the status of malaria in the world, revealing its existence as far north as Archangel (65°), U. S. S. R., and as far south as Córdoba, Argentina (32°). It occurs at altitudes of 9,000 ft (2,700 meters) in South America and central Asia, and below sea level in the Dead Sea area. The exact incidence of malaria is unkown, but 300,000,000 cases probably occur annually, with a mortality rate of about 1%. It probably is still the most prevalent serious illness of man.

The incidence of malaria in the United States and in certain other regions of the world began to decline long before the advent of modern therapeutic and preventive measures. The reduction of mosquito vectors by improvement and drainage of terrain was a factor in some instances, but mosquitoes in some areas where there is no malaria are as numerous as ever. Intensive application of chemicals to control the vectors and of drugs to control the disease will continue to reduce the incidence of the disease. The history of antimalarial therapy was discussed by Coggeshall.

According to four reports of the Council of Pharmacy and Chemistry in *The Journal of the American Medical Association* for Aug. 23, 1952, primaquine seems to be the drug of choice if used in combination with chloroquine for the treatment of acute attacks.

Toxoplasmosis.—Siim of Copenhagen reports seven instances in which toxoplasmosis was diagnosed in patients with obscure fever or lymphadenopathy. Six of the patients were children. None had symptoms referable to the eyes or central nervous systems, and each recovered. Toxoplasma bodies were not seen in tissues removed at biopsy or in cultures therefrom. Diagnosis was made solely by the Sabin-Feldman dye test and the complement-fixation test.[223] It is doubtful whether these procedures alone are reliable enough for definitive diagnosis.

In England a large-scale survey by means of intradermal and serologic tests revealed positive results for toxoplasmosis in insignificant numbers of children under 4 years of age, in 7% of children up to age 14, and in 17% over that age.[224]

222. Berberian, D. A., and others: Drug Prophylaxis of Amebiasis, J. A. M. A. **148**:700-704 (March 1) 1952.

223. Siim, J. C.: Acquired Toxoplasmosis: Report of 7 Cases with Strongly Positive Serologic Reactions, J. A. M. A. **147**:1641-1645 (Dec. 22) 1951.

224. Fisher, O. D.: Toxoplasma Infection in English Children: Survey with Toxoplasmin Intradermal Antigen, Lancet **2**:904-905 (Nov. 17) 1951.

Kala-Azar.—A case of kala-azar was studied in which infection probably took place in the Mediterranean area and disease began 34 months later.[225] As often happens, the time between inoculation and the onset of disease was regarded as the "incubation" period. This view probably is incorrect; the micro-organisms lay dormant but did not incubate for 34 months. In further respect to the misuse of the term, long incubation periods are described when malaria develops in persons months or years after infection.[226] Similar criticism may apply in three new cases of leprosy among relatives in a family in Norway which developed after exposure to a patient 20 years previously.[227]

Leprosy.—The chance of finding Mycobacterium leprae by examining scrapings of the skin is small. By applying Wayson's technic of examining the entire thickness of the skin, Maddock had more success. Myco. leprae was demonstrated in specimens of 19 preparations made from 84 patients previously considered as having arrested cases.[228]

Schistosomiasis.—While sodium pentachlorophenate ("santobrite") may eradicate almost all snails in infested water,[229] attempts to control schistosomiasis by killing Oncomelania nosophora only reduces their number temporarily and reduces the incidence of disease locally for a time. A few snails which survive soon repopulate the area. For thorough control, measures must be applied continually, including the use of molluscacides, sanitary engineering, education, prevention of water pollution, and treatment of victims.[230]

Filaria.—Nonsymptomatic microfilaremia due to Wucheria bancrofti was discovered in a veteran seven and a half years after exposure to infection in Samoa. Residuals of infection in 87 cases of filariasis in veterans consist chiefly of lymphadenopathy, usually axillary.[231]

In an editorial, syphilis is pointed out as often being a nonvenereal disease called bejel or balash in Asia and njovera in Africa. Other treponemal infections, pinta and yaws, are widespread in many regions of the world, and they together with the ones first named probably are as important as syphilis of venereal origin. The treponemal diseases are favorably influenced by therapy with penicillin, and excellent curative results are reported during programs of mass treatment of populations.[232]

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225. Stone, H. H.; Tool, C. D., and Pugsley, W. S.: Kala-Azar (Visceral Leishmaniasis): Report of a Case with 34 Month Incubation Period and Positive Doan-Wright Test, Ann. Int. Med. **36**:686-693 (Feb.) 1952.

226. Eddleman, E. E.; Hale, W. H., and Snowden, W. M.: Vivax Malaria with Long Incubation Periods: Report of 7 Cases, U. S. Armed Forces M. J. **2**:1693-1698 (Nov.) 1951.

227. Three New Cases of Leprosy in Norway, Foreign Letters, J. A. M. A. **148**:1050-1051 (March 22) 1952.

228. Maddock, R. K.: Skin Scrapings in Leprosy: Positive Results by the Wayson Technique in 84 Supposedly Arrested Cases, J. A. M. A. **148**:44-45 (Jan. 5) 1952.

229. Hunter, G. W., and others: Studies on Schistosomiasis: Control of the Snail Host of Schistosomiasis in Japan with Sodium Pentachlorophenate (Santobrite), Am. J. Trop. Med. & Hyg. **1**:831-847 (Sept.) 1952.

230. McMullen, D.: Schistosomiasis and Molluscacides, Am. J. Trop. Med. & Hyg. **1**:671-679 (July) 1952.

231. Conn, H. C., and Greenslit, F. S.: Filariasis Residuals in Veterans with Report of a Case of Microfilaremia, Am. J. Trop. Med. & Hyg. **1**:474-476 (May) 1952.

232. A Decade of Penicillin, Editorial, Am. J. Pub. Health **42**:306-307 (March) 1952.

MISCELLANEOUS

Cortisone and Corticotropin.—Neither cortisone nor corticotropin had an effect on the response of guinea pigs poisoned with the toxins of diphtheria or dysentery bacilli.[233] Previous conflicting reports on the influence of hormones on the febrile response to toxins are accounted for on variation in dosage. Large amounts of hormone cause significant suppression of the febrile and systemic response; small doses enhance the response.[234] Cortisone also suppressed or retarded the inflammatory response of animals to thermal injury [235] and to infection with pneumococci.[236] The effect was the same regardless of the cause of the inflammation and seems to depend on the influence of cortisone in maintaining better arteriolar tone. This effect does not favor an increased permeability of the vessels to permit diapedesis of leucocytes and thus does not enhance resistance to infection.[237] However, by using a special technique, investigators confirmed previous reports and showed that therapy with cortisone did not interfere with the development of antibodies. Patients with adrenal insufficiency, patients treated with cortisone, and normal persons responded alike to the injection of pneumococcic polysaccharide.[238]

The suppressive effect of hormones on the febrile and cellular response may be put to practical purposes for experimental investigation. Animals treated with cortisone and roentgen radiation are rendered susceptible to infection with a number of viruses and fungi against which they otherwise are resistant.[239] Perhaps by the application of this procedure, the agents of a number of infectious diseases which heretofore could not be transmitted to normal animals for investigation can be isolated. Success already has been attained with the pneumonia virus of mice [240] and a virus which causes hepatitis in mice.[94]

Blood Cultures.—In a critique on the methods of interpretation of cultures of the blood made in laboratories for diagnostic purposes, Kotin lists the following factors as causes of error: (1) the occasional presence of harmless bacteria in the

233. Murray, R., and Branham, S. E.: Effect of Cortisone and ACTH on Adrenals in Experimental Diphtheria, Shiga and Meningococcus Intoxication, Proc. Soc. Exper. Biol. & Med. **78**:750-753 (Dec.) 1951.

234. Duffy, B. J., and Morgan, H. R.: ACTH and Cortisone Aggravation or Suppression of Febrile Response of Rabbits to Bacterial Endotoxin, Proc. Soc. Exper. Biol. & Med. **78**: 687-689 (Dec.) 1951.

235. Moon, V. H., and Tershakovec, G. A.: Influence of Cortisone upon Acute Inflammation, Proc. Soc. Exper. Biol. & Med. **79**:63-65 (Jan.) 1952.

236. Germuth, F. G.; Ottinger, B., and Oyama, J.: The Influence of Cortisone on the Evolution of Acute Infection and the Development of Immunity, Bull. Johns Hopkins Hosp. **91**:22-48 (July) 1952.

237. Ebert, R. H., and Barclay, W. R.: Changes in Connective Tissue Reaction Induced by Cortisone, Ann. Int. Med. **37**:506-518 (Sept.) 1952.

238. Larson, D. L., and Tomlinson, L. J.: Quantitative Antibody Studies in Man: The Effect of Adrenal Insufficiency and of Cortisone on the Level of Circulating Antibodies, J. Clin. Invest. **30**:1451-1455 (Dec.) 1951.

239. Syverton, J. T., and others: Cortisone and Roentgen Radiation in Combination as Synergistic Agents for Production of Lethal Infections, Proc. Soc. Exper. Biol. & Med. **80**: 123-128 (May) 1952.

240. Smith, J. M.; Murphy, J. S., and Mirick, G. S.: Effect of Adrenal Hormones on Infection of Mice with Pneumonia Virus of Mice (PVM), Proc. Soc. Exper. Biol. & Med. **78**:505-510 (Nov.) 1951.

blood during health or with minimal trauma, (2) disregard of the potential pathogenicity of certain bacteria ordinarily believed to be harmless, (3) disregard of the seriousness of bacteremia in infants, (4) lack of correlation of bacteria with associated disease, (5) variations in technic of making cultures, and (6) failure to compensate in culture mediums for antibiotics or other agents given for therapeutic purposes. A seventh factor, of course, is contamination from faulty technic. Of 5,000 routinely made blood cultures, 13% gave positive results of which one-half had an unquestionable etiologic relationship to the disease. In the other half, bacteria were regarded as nonpathogens.[241]

Pigment-producing bacteria usually are nonpathogenic, but in rare instances when resistance is low they may be invasive and cause disease. Therapy with combinations of various antibiotics may control the infection for which they are given but may thereby allow the growth and invasion of antibiotic-resistant chromobacteria.[242] The subject was reviewed editorially but without mention of Gaffkya tetragena or Staphylococcus aureus, both makers of pigment.[243]

The literature about staphylococcic endocarditis was reviewed and 25 new cases were described. About 300 cases are estimated to occur each year in this country. Recovery accompanied therapy with penicillin in 47% of patients.[244]

Weed points out the importance of making an etiologic diagnosis of localized chronic lesions of bones, joints, tendons, and bursas. The tubercle bacillus still is the most common cause. Fungi and Brucella come next in order of frequency. E. typhosa is a rare cause.[245] The subject of brucellar arthritis of the hip joint was reviewed. Oxytetracycline was said to be of value in treatment.[246]

The general field of the mechanism of resistance to infectious agents was reviewed by Nungester.[247]

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241. Kotin, P.: Techniques and Interpretation of Routine Blood Cultures: Observations in 5,000 Consecutive Patients, J. A. M. A. **149**:1273-1276 (Aug. 2) 1952.

242. Wheat, R. P.; Zuckerman, A., and Rantz, L. A.: Infection Due to Chromobacteria: Report of 11 Cases, A. M. A. Arch. Int. Med. **88**:461-467 (Oct.) 1951.

243. Infection Due to Chromobacteria, Editorial, J. A. M. A. **148**:56 (Jan. 5) 1952.

244. Dowling, H. F., and others: Staphylococcic Endocarditis: Analysis of 25 Cases Treated with Antibiotics, Together with Review of Recent Literature, Medicine **31**:155-176 (May) 1952.

245. Weed, L. A.: Importance of Bacteriology in Orthopedic Surgery, Proc. Staff Meet., Mayo Clin. **27**:225-230 (June 4) 1952.

246. Bergsagel, D. E.; Beamish, R. E., and Wilt, J. C.: Brucella Arthritis of the Hip Joint: A Review of the Literature and Report of a Case Treated with Terramycin, Ann. Int. Med. **37**:767-775 (Oct.) 1952.

247. Nungester, W. J.: Mechanisms of Man's Resistance to Infectious Diseases, Bact. Rev. **15**:105-130 (Sept.) 1951.

Case Reports

ACUTE INTERMITTENT PORPHYRIA

Prompt Response to Therapy with Corticotropin

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THERE have been an increasing number of case reports of the hitherto comparatively rare group of disorders included under the general term of porphyria. An excellent review of the recent literature may be found in the publications of Goldman and Kaplan [1] and of Calvy, Jaruszewski, and Carroll.[2] In all the case reports it may be noted that the treatment of this severe disorder has been entirely nonspecific and has been directed primarily toward the correction and amelioration of the distressing symptoms of the disease, particularly pain and fluid imbalance.

This report concerns itself with a case of acute intermittent porphyria of the "mixed" variety, combining the features of the light-sensitive and the acute type. It is noteworthy, as it presents the first recorded case in which dramatically successful therapy was accomplished with adrenocortical hormone.

A 39-year-old Englishwoman was first observed by us on Sept. 21, 1952, with a three-day history of rapidly progressing nausea, vomiting, inability to tolerate food or fluids, obstipation, and severe epigastric pain radiating to the back and to both flanks. Associated with these symptoms was the passage of a scanty volume of black urine.

The patient had left England five weeks before to join her husband in the British West Indies. While there she spent several hours of each day in the bright sunlight. There was no history of the ingestion of barbiturates. She was entirely asymptomatic until the onset of abdominal pain and vomiting on Sept. 17, 1952. After supportive and narcotic therapy in the British West Indies had failed to provide her with any relief, she was advised to return to England. She arrived in New York City by plane from the British West Indies on Sept. 21, but her condition was deemed too poor to permit her to continue the anticipated flight to England, and she was hospitalized.

In January, 1951, the patient had been hospitalized in England because of acute porphyria attributed to the ingestion of barbiturates. Her symptoms and physical findings at that time were so severe that she remained in the hospital for three months, receiving intensive supportive therapy, which produced only a gradual amelioration of symptoms. After this hospitalization, for several months she was only partially ambulatory at home, during which time her symptoms of abdominal pain, vomiting, and constipation gradually disappeared.

During this first hospitalization for acute porphyria, in England, it was noted [3] that neurological and psychiatric symptoms were prominent in addition to the bizarre extensive symptoms characteristic of the present episode. She was observed to manifest horizontal nystagmus and a slight degree of astereognosis and hyperesthesia over the abdomen and upper third of the

From the Medical Department, Lever Brothers Company, New York 22.

1. Goldman, A. M., and Kaplan, M. H.: Acute Porphyria, Ann. Int. Med. **34**:415-427 (Feb.) 1951.

2. Calvy, G. L.; Jaruszewski, E. J., and Carroll, H. H.: Porphyria: Clinical Observations and a Family Vignette, Ann. Int. Med. **34**:767-777 (March) 1951.

3. This information was supplied by Dr. W. N. Rogers, St. Heliers Group of Hospitals, Surrey, England.

thighs. The electroencephalogram revealed abnormal slow activity which gradually returned to normal over a period of two months. Weakness and slight atrophy of the first dorsal interosseus muscles were also noted.

Laboratory studies revealed total urine porphyrins of 5 mg. per liter (porphobilinogen 1.5 units per cubic centimeter). Serum electrolyte studies reflected the patient's dehydrated state; a serum bilirubin content of 1.4 mg. per 100 cubic centimeters was present. The blood pressure was elevated during that first acute phase to 150/100 but returned to normal levels after two to three months, along with the gradual subsidence of symptoms.

The patient's family history is significant in that her sister was studied in the course of a family survey and was observed to have porphyrinuria which has not become symptomatic.

The patient was acutely ill at the time of our initial observation and presented symptoms of very severe upper abdominal pain which radiated to the back, to both flanks, and to the anterior chest. Nausea and vomiting were persistent; she had been unable to take any food or fluids by mouth for three days. Generalized headache was present. She complained of itching, burning, and tingling of the finger tips and both posterior thighs. There had been no bowel movement since the onset of the present episode.

The patient was markedly dehydrated. She presented scattered vesicular lesions and scars of old lesions on the face and exposed part of the chest which resembled those of epidermolysis bullosa. She was depressed, lethargic, and extremely apprehensive. The temperature was slightly elevated, to 99.4 F. (oral); the blood pressure was 140/100. The deep tendon reflexes in both lower extremities were markedly hyperactive. The abdomen was soft, with mild tenderness on deep epigastric palpation. A conspicuous physical finding was the ready elicitation of a marked dermographia with whealing induced by light skin stroking, particularly marked over the abdomen. The patient had no previous history of allergy or urticarial episodes.

Efforts were made to correct the dehydration by administration of fluids and electrolytes parenterally. Morphine and meperidine hydrochloride (demerol®) were required to produce even a mild degree of relief from pain. Her urine contained porphyrins, but the remainder of her blood, urine, and serum electrolyte studies reflected only the patient's dehydrated state, and the values promptly returned to normal limits after several days of intensive therapy with parenterally given fluids with electrolytes. The patient also received large daily doses of liver extract, vitamins, and calcium gluconate.

Water and mineral balance was achieved within three days after her hospital admission, but the patient continued to manifest elevated temperature, elevated blood pressure (ranging to 170/110), very severe abdominal pain, persistent nausea and vomiting, anorexia, obstipation, and tachycardia. Her narcotic requirement increased with the passage of time, and these drugs produced only transient, partial relief from pain and insomnia. The paresthesias, hyperreflexia, and mildly disturbed emotional state remained unchanged, as did the conspicuous dermographia.

In view of the possibility of an allergic component being present in this disorder, as manifested by the dermographia and a rather high eosinophile count (466 per cubic millimeter) it was decided to employ corticotropin on a probatory basis in an effort to effect an improvement in the persistent distressing symptomatology.

The patient was given 40 units of corticotropin ("acthar") gel each eight hours beginning on the fourth hospital day. Within a period of 12 to 24 hours there was a striking and dramatic improvement in her clinical status. The improvement continued for the next three days under this regimen with the result that nausea and vomiting disappeared entirely, oral intake of food and fluids was well tolerated, and the first spontaneous bowel movement occurred. The abdominal pain subsided somewhat more slowly, but the patient required only a small fraction of her previous doses of narcotics to achieve complete relief. The urine became progressively lighter in color from the original black but continued to contain porphyrins, on which no quantitative studies were available. The temperature returned to normal on the second day of corticotropin treatment, and the blood pressure dropped to the previous normal level of 130/80. The eosinophile count was reduced to 150 per cubic millimeter (originally 466 per cubic millimeter), indicating a response to the corticotropin. Rounding of the facial contour, mild facial hirsuties, and mild follicular dermatitis of the face were observed during the first week of corticotropin administration.

The patient was remarkably encouraged by the striking improvement in her status and became cheerful and enthusiastic over the prospects for her recovery. The dermographia disappeared almost entirely two days after the institution of corticotropin therapy. The patient was anxious to return to her home in England; hence we were unable to follow her future course by our direct observation. Through correspondence [3] we have learned that her trip was uneventful and her favorable course continued with rapidly decreasing doses of corticotropin. She remained hospitalized in England for 12 days more of therapy, during which time her eosinophile counts varied from 0 to 89 per cubic millimeter.

She received a dose of 680 units of corticotropin over a period of 6 days in New York and an additional dose of 370 units over a period of 12 days in England. The total dose of 1,050 units of corticotropin produced a complete remission in this case of severe mixed acute intermittent porphyria which presented a combination of symptoms and signs involving skin, viscera, and nervous system.

COMMENT

The rationale for therapy with corticotropin was based on the patient's presentation of a syndrome resembling to a certain extent a hypersensitivity syndrome, indicated by physical allergy (to sunlight) and by traumatic allergy (dermographia from skin stroking). Some of the beneficial effects of the therapy might be attributed to the well-known euphorigenic action of corticotropin. It is not likely that this action alone was responsible for the strikingly salutary effects on the objective evidences of the disorder.

One previous attempt at treatment of acute porphyria with corticotropin has been reported.[4] Here, despite seemingly adequate dosage (80 to 100 mg. per day) as measured by the eosinophile response, the drug was ineffective. None of the physiologic side-effects were observed in the case of Oltman and Friedman, however; whereas in ours a rapid development of "Cushingoid" features was achieved. This rapid approach to a physiologic limit is believed by some to be the optimal method for producing a remission in acute disseminated lupus erythematosus.[5] Future experience may demonstrate that in acute porphyria, too, maximal suppression can be achieved only when clinical hyperadrenocorticism is induced.

This case is presented in the hope that it will serve as a stimulus to further use of corticotropin or cortisone in the treatment of this severe disorder, which frequently carries with it a rather poor prognosis.

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4. Oltman, J. E., and Friedman, S.: Acute Porphyria: Report of a Case Showing Ineffectiveness of ACTH, New England J. Med. **244**:173-174 (Feb.) 1951.

5. Dubois, E. L.; Commons, R. R.; Starr, P.; Stein, C. S. Jr., and Morrison, R.: Corticotropin and Cortisone Treatment for Systemic Lupus Erythematosus, J. A. M. A. **149**:995-1002 (July 12) 1952.

PROLONGED VENTRICULAR TACHYCARDIA

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PROLONGED ventricular tachycardia is still a rather infrequent occurrence and therefore warrants a report of cases. The longest case on record was reported by B. Moia and M. Campana,[1] who state that it lasted for 123 days, ending fatally. Large doses of quinidine were administered intravenously. Most of the cases reported varied in duration from 11 to 77 days. Invariably, all cases lasting over 20 days ended fatally.

We shall review briefly some of the reports concerning prolonged ventricular tachycardia. Vakil and Vahia [2] reported on a 38-year-old man, a Moslem, with ventricular tachycardia which continued without intermission for 20 days and terminated abruptly after intensive quinidine therapy.

Porter [3] in 1924 reported a case lasting six days, with recovery. The patient had an underlying myocardial infarction. Levine and Fulton [4] reported a fatal case of ventricular tachycardia in which the paroxysm continued for 14 days. Salley [5] in 1932 cited a fatal case of 11 days' duration. Subsequent cases were reported in 1934 by Elliott and Fenn [6] and in 1940 by Strong and Munroe.[7] The latter authors described ventricular tachycardia in a man of 41 which lasted for 23 days without intermission and responded dramatically to 40 grains (2.59 gm.) of quinidine sulfate administered intravenously. This case is the longest with recovery on record.

In 1942 Mays [8] reported a case of ventricular tachycardia of 77 days' duration. The patient was a 59-year-old Polish cabinetmaker. Tachycardia lasted 77 days

From the Medical Service of Dr. Irwin Stillman, Coney Island Hospital.

1. Moia, B., and Campana, M.: Fatal Ventricular Tachycardia of 123 Days' Duration Treated with Large Doses of Intravenous Quinidine, Rev. argent. cardio. **13**:334-346 (Jan.-Feb.) 1947.

2. Vakil, R. J., and Vahia, N. S.: Ventricular Tachycardia of Long Duration (20 Days) with Recovery, Indian M. Gaz. **79**:349-351 (Aug.) 1944.

3. Porter, W. B.: Paroxysmal Ventricular Tachycardia: Report of a Case Lasting 153 Hours with Recovery, Am. J. M. Sc. **167**:821-827 (June) 1924.

4. Levine, S. A., and Fulton, M. N.: Effect of Quinidine Sulphate on Ventricular Tachycardia: Clinical Observations, J. A. M. A. **92**:1162-1168 (April 6) 1929.

5. Salley, S. M.: Unusual Atropin Effect on Ventricular Tachycardia, Am. J. M. Sc. **183**:456-457 (April) 1932.

6. Elliott, A. R., and Fenn, G. K.: Long Continued Ventricular Tachycardia: Report of Unusual Case, Am. Heart J. **9**:806-812 (Aug.) 1934.

7. Strong, G. F., and Munroe, D. S.: Paroxysmal Ventricular Tachycardia with Report of Unusual Case, Am. Heart J. **19**:486-491 (April) 1940.

8. Mays, A. T.: Ventricular Tachycardia of Unusually Long Duration (77 Days), Am. Heart J. **23**:119-127 (Jan.) 1942.

in spite of medical treatment. The patient received 22½ grains (1.45 gm.) of digitalis, several injections of acetyl-β-methylcholine chloride with carotid-sinus pressure, one intravenous injection of magnesium sulfate, two intravenous injections of quinine dihydrochloride, and three intravenous injections of quinidine sulfate. Postmortem examination revealed coronary thrombosis with infarction and intraventricular-septum involvement.

In nearly all cases of prolonged ventricular tachycardia with underlying myocardial infarction, the outcome was fatal in spite of therapy. Patients with no organic heart disease had a favorable prognosis.

REPORT OF CASE

A. S., a 50-year-old white man of Russian descent, a cashier, was admitted to Coney Island Hospital on March 30, 1951, with the chief complaint of pain in the left chest, pressing in character, limited chiefly to the sternal area, of several hours' duration. The pain radiated to the left shoulder and was associated with nausea and dyspnea. Shortly after the onset of pain, he became cold and clammy.

The patient's history and the family history were not significant.

On admission, the patient appeared to be a middle-aged white man acutely ill, ashen-gray, and dyspneic. The temperature was 100.4 F., pulse rate 80 per minute, blood pressure 90/60, and respirations 24 per minute. There was normal hair distribution, the skin was cold and clammy, and some cyanosis of the lips and nail beds was present. The pupils were equal and regular and reacted to light and in accommodation; there was no nystagmus. The ears, nose, and throat were essentially normal. The neck revealed no rigidity, no masses, and no venous distention; the trachea was in the midline, and no abnormal pulsations were noted.

The chest was symmetrical; the heart did not appear to be enlarged on percussion. The point of maximum impulse was difficult to determine; sounds were of poor quality; sinus rhythm was regular, and no murmurs were audible. Examination of the lungs revealed a few crepitant rales at both bases but otherwise no significant physical findings. The abdomen was on chest level; there were no abnormal pulsations; the liver, spleen, and kidneys were not felt; a Murphy test was negative. Rectal examination revealed no external hemorrhoids. No further examination was done in view of the patient's critical condition. The extremities showed no edema or varicosities. The reflexes were physiological throughout.

The clinical impression was that the patient had an acute myocardial infarction. An electrocardiogram (Fig. 1) taken on March 3 suggested one of the early phases of acute myocardial infarction involving the posterior basilar portion of the left ventricle. The patient was treated with the usual routine, namely, bed rest, sedation, and oxygen and anticoagulant therapy. His condition showed no essential change until April 2, at which time a marked pallor developed and he appeared gravely ill. Examination of the heart revealed the sounds to be of poor quality, gallop rhythm was audible at the apex, and the rate was 160 per minute. There were fine and coarse crepitant rales at the bases of both lungs. The abdomen was soft; there were no masses; the liver, spleen, and kidneys were not felt, and a Murphy test was negative. The extremities showed no peripheral edema. It was felt that the patient had a ventricular tachycardia. The diagnosis was supported by electrocardiogram (Fig. 2). He was immediately given oxygen by BLB mask and 500 mg. of procaine amide ("pronestyl") hydrochloride intravenously. This caused the rate to slow somewhat, but ventricular tachycardia persisted. Another 500 mg. of procaineamide was given without avail. On April 3 the blood pressure fell to 80/?, and he appeared to be in shock. He was given 250 cc. of plasma intravenously and ⅙ grain (10 mg.) of morphine sulfate. Administration of quinidine sulfate, 6 grains (0.39 gm.) every three hours, was started. On April 5 his blood pressure was 100/80, and administration of quinidine was continued every three hours without any significant change in the electrocardiographic tracing (Fig. 3). On April 6 the dose of quinidine was increased to 10 grains (0.65 gm.) every three hours, but

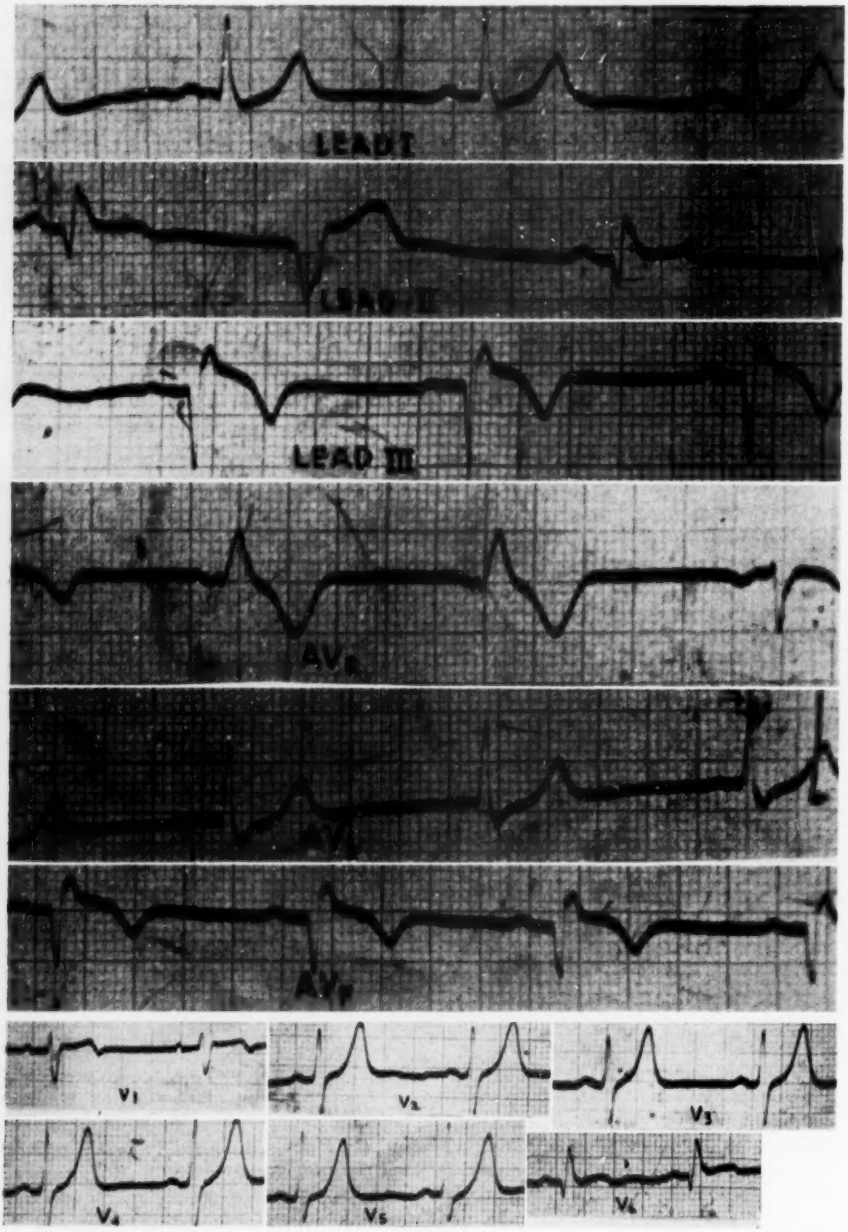

Fig. 1.—A stage of recent myocardial infarction involving posterior basilar portion of left ventricle. Changes in V_6 indicate extension to lateral wall. An occasional premature ventricular contraction may be noted.

because of vomiting and tinnitus its use was discontinued late that day. He was given 1,000 cc. of 10% dextrose in saline intravenously and pronestyl hydrochloride, 1 gm. four times a day. On April 7 his blood pressure was 95/70, and on April 8, in addition to the procaine amide

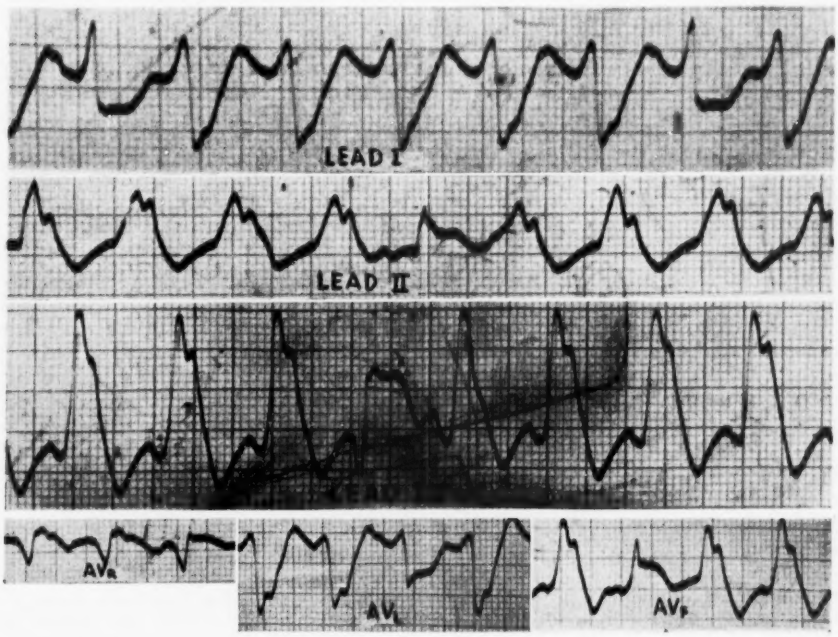

Fig. 2.—Paroxysmal ventricular tachycardia complicating posterior-wall infarction. Periodical occurrence of regular sinus beats may represent parasystolic rhythm. Ventricular rate is over 150 a minute.

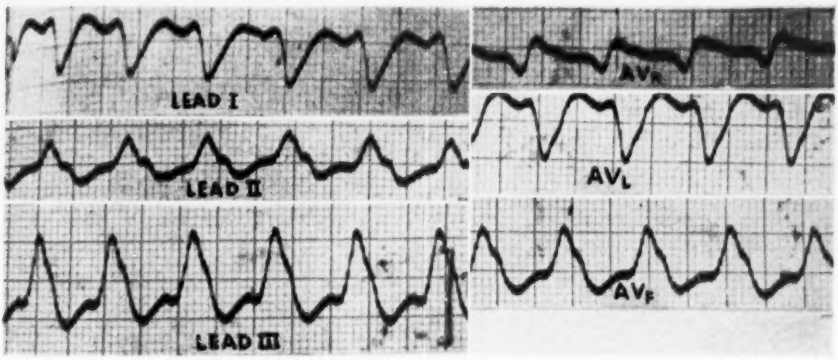

Fig. 3.—A further stage of paroxysmal ventricular tachycardia. Rate is unchanged.

("pronestyl") hydrochloride, administration of papaverine hydrochloride, 3 grains (0.19 gm.) every three hours, was begun. A tracing on April 9 revealed the electrocardiogram to be unchanged (Fig. 4). On April 10, he was again given 10 grains (0.65 gm.) of quinidine sulfate

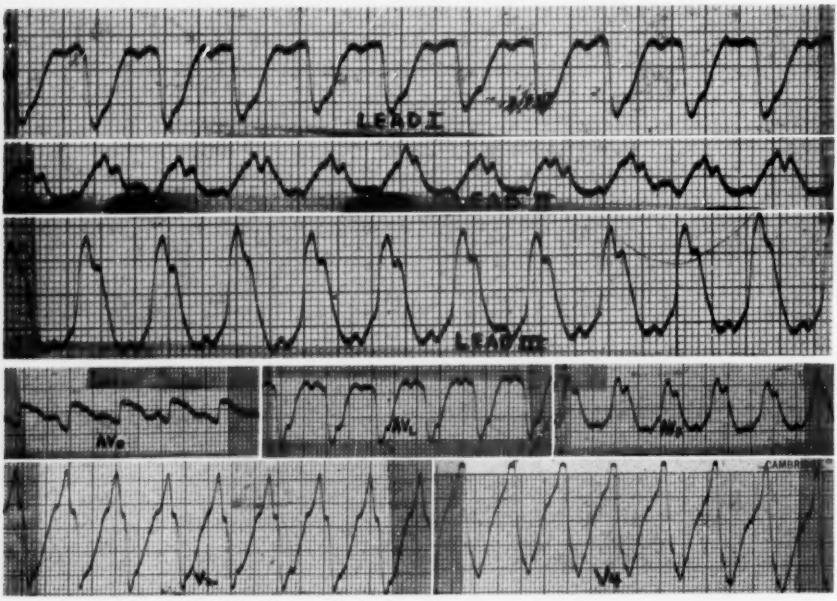

Fig. 4.—Paroxysmal ventricular tachycardia of seven days' duration. Ventricular rate is unchanged. QRS complexes are wider and more bizarre in configuration. QRS is 0.32 second.

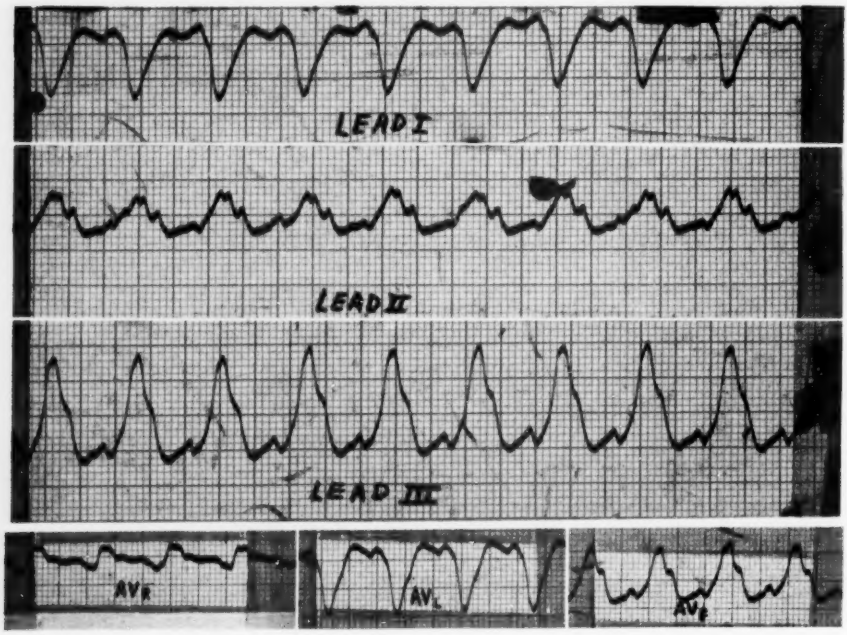

Fig. 5.—Paroxysmal ventricular tachycardia of 12 days' duration. Rate is unchanged.

every three hours and also neostigmine (solution prostigmine methylsulfate® 1:2,000) three times a day. On April 12 administration of large doses of potassium iodide was begun and the following day he received 250 cc. of 1% procaine hydrochloride solution intravenously. At the onset of the coronary occlusion, bishydroxycoumarin (dicumarol®) therapy was instituted, and it was maintained. The patient also received magnesium sulfate intravenously.

On April 14 the patient began to show more signs of congestive heart failure (Fig. 5), requiring daily injections of meralluride sodium (mercuhydrin sodium®). Penicillin was also given as a prophylactic measure. From April 20 until April 22 he was given sedation in the form of phenobarbital (luminal®). On April 24, his liver became markedly enlarged and he went into acute left-ventricle failure, with pulmonary edema, and died. The electrocardiographic changes remained the same from April 2 until death, indicating a total of 23 days of ventricular tachycardia.

Laboratory Data.—On April 3 the red cell count was 3,500,000, the hemoglobin content 12 gm., and the white cell count 8,000, with 64% polymorphonuclear leucocytes, 24% lymphocytes, and 12% eosinophiles. On April 9 the count was 3,450,000 red cells, 10 gm. hemoglobin, and 10,000 white cells, with 84% polymorphonuclear leucocytes and 16% lymphocytes. Urinalysis was essentially negative. Tests of the serum were negative. Blood glucose was 105 mg. and blood urea nitrogen 23 mg. per 100 ml. The erythrocyte sedimentation rate varied from 24 to 30 mm. in one hour. The icteric index was 20, and the bishydroxycoumarin level was maintained at two and one-half times the normal level.

Postmortem Examination.—Consent for autopsy limited to exploration of the thoracic cavity was obtained. Postmortem examination was performed one-half hour after death. The body was that of a 50-year-old, well-developed, well-nourished, white man. There was generalized cyanotic mottling of the face and the neck. The neck veins were markedly distended. There was no peripheral edema. The pleural cavities each contained 500 cc. of straw-colored fluid. The pleural linings were grayish-pink, smooth, and glistening, and there were a few adhesions of the visceral and parietal pleura of the left lung posteriorly. The pericardial cavity contained 80 cc. of straw-colored fluid. The heart lay free in the pericardial cavity and was enlarged, the apex being in the sixth left intercostal space at the midclavicular line. The heart weighed 475 gm. The epicardium was smooth and glistening except for an area 4 cm. in diameter over the posterior wall of the left ventricle near the apex, where the surface was somewhat dull and showed multiple subepicardial petechial hemorrhages. The myocardium in this region was softened and thinned. On opening of the heart, the auricles were seen to be smooth and free of thrombi. The tricuspid valve measured 11 cm. in circumference. The valve leaflets were thin, smooth, and translucent, with discrete chordae tendineae. The wall of the right ventricle measured 0.4 cm. in diameter. The pulmonary valve measured 8 cm. in circumference, and the valve leaflets were smooth and translucent. The mitral valve measured 10.5 cm. in circumference; the valve leaflets were thickened and contained many small nodules along their free borders. The chordae tendineae were shortened and moderately thickened and showed some fusion. The two posterior papillary muscles were yellow-tan and showed marked softening. The endocardium of the left ventricle posteriorly, corresponding to the area of softening and surface petechiae previously described, presented a dull, somewhat roughened, deep-red to mahogany-brown appearance, which extended to involve the posterior-inferior portion of the interventricular septum. Serial sections through the posterior papillary muscles and adjacent portions of the left ventricle showed the myocardium to be yellowish-tan, with many areas of necrosis and old hemorrhage (Figs. 6 and 7). Elsewhere the myocardium was reddish-brown and streaked with dull, grayish areas of fibrosis. The aortic valve measured 7 cm. in circumference. There was fusion of the cusps at their bases, but the valve leaflets were thin and pliable, with nodular thickenings along their free edges. There was some atherosclerosis at the base of the aortic valves, and 1.5 cm. above the valve the intima showed a sclerotic plaque measuring 2.5 cm. in diameter, in the center of which was a punched-out ulcer measuring 1 by 0.5 cm.

Examination of the coronary vessels revealed complete occlusion of the lumen of the right coronary artery by a thrombus starting 1 cm. from its origin and extending along the vessel for a distance of 2 cm. (Figs. 7 and 8).

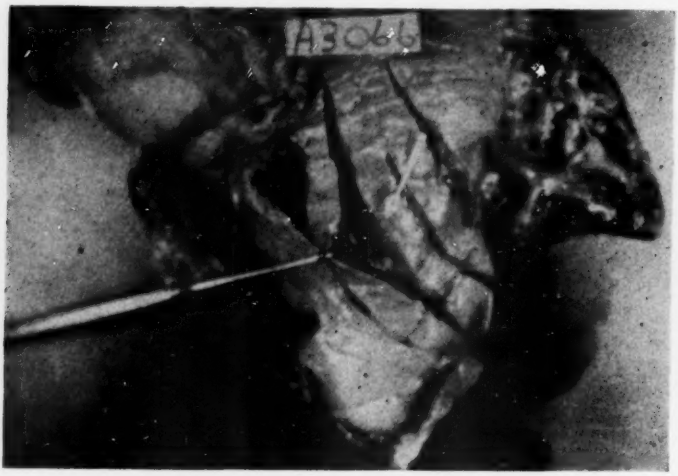

Fig. 6.—Section through posterior wall of left ventricle, showing hemorrhage and necrosis of myocardium.

Fig. 7.—Enlargement of area of posterior wall of left ventricle, showing hemorrhage and necrosis of myocardium.

Fig. 8.—Section of right coronary artery. Arrow points to vessel shown in cross section, with thrombus completely occluding lumen.

Fig. 9.—Enlargement of Figure 8.

Serial sections through the artery showed pronounced calcific atherosclerosis. Section of the left coronary artery disclosed atherosclerotic narrowing of the lumen, particularly in the left anterior descending branch. At some points along its course, a fine probe could be passed with difficulty.

The lungs were smooth and mottled pinkish-gray and black. Both upper lobes and the right middle lobe were well aerated. The lower lobes, particularly in the posterior portions, were fleshy and showed loss of normal crepitation. On section, the cut surfaces revealed marked congestion, and a red frothy fluid exuded. The trachea and bronchi were filled with a frothy pink fluid.

The abdominal viscera were inspected through an incision in the diaphragm. The peritoneal cavity contained a large amount of clear straw-colored fluid. The liver was enlarged to 5 cm. below the right costal margin. Its surface was smooth and dark-red. A small section taken for study revealed a prominent nutmeg pattern. The spleen was enlarged to 3 cm. below the left costal margin. Its cut surface presented a deep-red pulp, with increase of the trabeculae and prominent lymphoid follicles.

Histological Examination.—Heart: Sections from the posterior part of the interventricular septum and from the posterior wall of the left ventricle showed almost complete destruction of the myocardium, with replacement by a vascular fibrous tissue. In some areas the capillarization was so intense as to approach granulation tissue in appearance. There were focal collections of polymorphonuclear leucocytes infiltrating areas of granular degenerated muscle fibers. Throughout, there was diffuse infiltration of lymphocytes, plasma cells, and pigment-laden macrophages, as well as extravasated blood pigment. In other areas, small isolated groups of muscle fibers were present which showed fragmentation and loss of cross striation. The fibrils were swollen and wavy. The nuclei were lost for the most part. Those which remained showed varying degrees of chromatolysis. The areas of remaining muscle fiber were surrounded by the vascular fibrous tissue. Elsewhere, fibers were separated by edema fluid, and there were broad areas replaced by fibrous tissue.

Coronary Vessels: There was a large arteriosclerotic plaque within the wall of the coronary artery which had a laminated thrombus adherent to it. There was evidence of recanalization. The media showed fragmentation, and there was deposition of calcium within this coat. The left anterior descending coronary artery showed evidence of atherosclerosis. The smaller vessels showed marked thickening of the intima with encroachment upon the lumen. There was reduplication of the internal elastic lamina. The ascending aorta revealed extreme widening of the intima, with hyaline deposition. The elastic tissue of the media was frayed. There were focal collections of lymphocytes and plasma cells which were not related to the vasa vasorum.

Lungs: Sections from the lower lobes showed large areas of atelectasis, with thickening of the alveolar walls. In other areas, the septa were broken down, leaving large emphysematous spaces. Elsewhere, the alveolar spaces were filled with amorphous debris, lymphocytes, and large macrophages containing pigment. The alveolar capillaries were prominent and engorged.

Spleen: The capsule was intact, and broad trabeculae coursed through the substance of the spleen. The sinusoids showed marked engorgement. There was considerable free pigment. The major vessels showed thickening of the intima, with narrowing of the lumina.

Liver: There was a mosaic of swollen liver cords surrounding the central veins. The sinusoids were dilated, and the subendothelial space was prominent. The liver cells showed cloudy swelling and granulation, with indistinct cell borders, in the central portions of the lobule. At the periphery of the lobule, the cell integrity was normal. The portal triads were intact, but there was a moderate lymphocytic infiltration. Glisson's capsule was intact.

The number of cases of myocardial infarction complicated by prolonged and intractable ventricular tachycardia in which the patient survived is almost nil. This case demonstrates the length of time the heart is capable of running a "marathon," so to speak, in spite of massive myocardial infarction.

In case of ventricular tachycardia, certainly, multiple methods of therapy lend themselves to use. Quinidine seems to be the drug of choice, for it is this drug

that is of foremost importance in the treatment of ventricular tachycardia in the course of coronary occlusion.

In this case many of the cardiac depressants were used, namely, quinidine, digitalis, procaine amide hydrochloride, and magnesium sulfate. None apparently had any effect on the cardiac rhythm. This observation may be assumed to have been due to a number of factors. First, the extent of myocardial infarction was too great, putting the cardiac muscle into a highly irritable state. Second, there was almost complete destruction of cardiac muscle, with replacement by a vascular fibrous tissue in the posterior portion of the interventricular septum and in the posterior wall of the left ventricle. Thus, one can see that any drug would have been almost useless in its action. Third, in addition to massive and complete posterior-wall necrosis, the blood supply to the anterior wall of the heart was insufficient, as demonstrated by atherosclerosis of the left descending coronary artery and marked replacement fibrosis. There was generalized atherosclerosis of the other collaterals. So the heart was almost completely ischemic, highly irritable, necrotic, and incapable of responding to drug therapy simply because its muscular and nervous mechanism was destroyed. Indeed, the heart was actually beating because of its own inherent mechanism and was not controlled by any part of the conduction system.

The length of survival was unusually long in view of the pathological findings.

SUMMARY AND CONCLUSIONS

A review of the literature reveals that ventricular tachycardia is usually fatal when complicating coronary thrombosis and lasting over 10 days.

A case of ventricular tachycardia of 23 days' duration, which ended fatally, is presented.

There was no change in rhythm depite therapy with the usual drugs.

The pathological findings indicated the extensiveness of myocardial damage in spite of the relatively long survival.

The importance of early and adequate quinidine therapy is discussed, together with some of the possible reasons for physiological failure of the drug.

PARADOXICAL RESPONSE TO CAROTID SINUS PRESSURE IN CHAOTIC HEART RHYTHM

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AND
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IT IS WELL known that carotid sinus pressure in paroxysmal auricular tachycardia usually reverts the arrhythmia suddenly to normal sinus rhythm. Auricular flutter may be slightly and temporarily slowed by carotid sinus pressure, or there may be a sharp reduction in rate due to induced heart block. However, sinus rhythm is not thereby restored, as it is in auricular tachycardia. The production of regular sinus rhythm by carotid pressure during auricular flutter has not been reported, to our knowledge.

Chaotic heart rhythm results from the irregular disorderly discharges of numerous ectopic foci located in the auricles, the auriculoventricular node, and the ventricles. It is usually associated with advanced heart disease or digitalis intoxication. It is a serious prognostic sign and is often associated with sudden death. Physiologically, it represents a depression of the normal pacemakers of the heart and the dominance of various ectopic foci.[1]

The following case is one of a bizarre chaotic rhythm occurring as a paroxysmal heart action in an apparently healthy young soldier, who showed no other discernible evidence of organic heart disease. The dominant rhythmic pattern was that of flutter with varying block, which was temporarily converted to normal sinus rhythm by carotid sinus pressure and reverted to flutter when the pressure was released.

REPORT OF A CASE

W. H. B., a 25-year-old soldier, with almost three years in military service, was admitted to an Army station hospital after a bout of paroxysmal cardiac arrhythmia. The past personal and family histories were not contributory, except that the patient's mother died of heart disease at 56 years of age. The patient was unmarried. He used no alcohol, tobacco, or drugs and had been an active farmer before his induction into military service. Five years prior to admission, he had had frequent bouts of palpitation characterized by sudden onset and termination. He was treated by his local physician, and the attacks subsequently disappeared. Two years before the present admission the bouts recurred, infrequently at first, and the patient carried on with his military duties. However, shortly before his hospitalization the attacks of "palpitation with skipped beats of the heart" became more frequent and severer. On the day of admission the patient had a sudden acute attack of palpitation, with a completely regular heart rate of 180 per minute, which was stopped at an army dispensary by carotid sinus pressure. He felt better on entering the hospital but complained of a sensation of skipping of the heart.

1. Katz, L. N.: Electrocardiography Including an Atlas of Electrocardiograms, Philadelphia, Lea & Febiger, 1941.

Examination on admission revealed a thin, asthenic, nervous, and cooperative person, who weighed 131 lb. (59.5 kg.) and was 5 ft. 9 in. (175 cm) tall. The only significant findings were multiple premature contractions, which tended to disappear on exercise. The heart tones were of good quality, with a rate of 100 per minute. No murmurs were audible, and the blood pressure was 122/78. There was a normal cardiac reserve as judged by standard exercise-tolerance tests. The impression on admission was that the condition was paroxysmal auricular tachycardia with multiple premature contractions in an emotionally tense person.

Laboratory Studies.—The urine had a specific gravity of 1.018; tests for acid, sugar, and albumin were negative. Microscopic examination showed occasional epithelial cells. Blood studies showed hemoglobin, 15 gm., normal morphology of red blood cells, a white blood cell count of 5,200, and a differential count of 3% stab cells, 55% segmented cells, 40% lymphocytes, and 2% monocytes. The sedimentation rate was 1 mm. in one hour (Westergren method). A Kahn test for syphilis was negative. The basal metabolic rate was —2%. A teleroentgenogram of the chest demonstrated no significant abnormality of the cardiac silhouette, and both lung fields were clear. Cardiac fluoroscopy showed a bathycardia, consistent with the patient's habitus. The pulmonary conus was slightly prominent, but this was not thought to be significant. There was no chamber enlargement in any position.

Course in the Hospital.—For the first week after admission, the patient felt perfectly well, manifesting only an occasional premature contraction. On the eighth hospital day he had an attack of paroxysmal arrhythmia. On examination many rhythms were heard. There were showers of extrasystoles followed by total irregularity of the heart, which did not disappear on exercise. On one occasion a run of regular tachycardia at a rate of 160 per minute was heard at the apex. This run was not stopped by carotid sinus pressure or eyeball pressure. The heart did slow but then resumed its rapid rate. Interspersed with this rapid rate were many premature contractions. When the apical rate was counted a second time, the rate was 150 per minute. These findings were interpreted clinically as more consistent with auricular flutter than with paroxysmal auricular tachycardia. The electrocardiogram taken at this time is discussed below.

The following day, because of a recurrence of the arrhythmia, the patient was given quinidine. Three hours after one dose of 0.2 gm. the rhythm became regular at a rate of 80 per minute. Regular sinus rhythm with a rate between 60 and 80 per minute was maintained for the next nine days. On the 18th hospital day another episode of paroxysmal arrhythmia occurred. An electrocardiogram taken at this time showed flutter with varying block and multiple premature contractions. Regular sinus rhythm was established but this time with showers of premature contractions. These did not cause any distress or symptoms. On the 24th hospital day the patient received a medical discharge from the Army.

Discussion of Electrocardiogram.—The accompanying electrocardiogram (Figs. 1, 2, 3, and 4), taken on the eighth day, is a continuous tracing made during a paroxysmal bout of arrhythmia. Fundamentally, it represents a flutter mechanism with sufficient variations to produce a chaotic heart action. The prime interest, however, is in the effect of carotid sinus pressure. On three separate occasions vagal stimulation by carotid sinus pressure converted auricular flutter to normal sinus rhythm. Soon after the release of the carotid sinus, the original flutter mechanism was reestablished. Throughout the tracing varying foci of irritability are demonstrable. Premature contractions occur rarely in auricular flutter, but in this tracing there are many.

In Figure 1*A* are shown premature contractions arising from many foci, both auricular and ventricular. Figure 1*B* shows the dominant auricular flutter rhythm, interspersed with ectopic foci, merging into a flutter-fibrillation and showing two successive ventricular premature contractions. Figure 1*C* at first glance can be interpreted as nodal tachycardia. However, in view of the apparent flutter at *D*, the probability is that there is a flutter all the way through. A possible mechanism is dissociation, with auricular flutter wave gradually pulling away from the ventricular complex. The decision between the diagnosis of paroxysmal tachycardia and that of auricular flutter is sometimes arbitrary, and transitions probably exist. According to Katz,[1] if the rapid heart action is chronic the rhythm is usually flutter and if it is paroxysmal nothing practical is gained from making the distinction. Figure 1*E* shows a succession of three ventricular premature contractions. Figure 1*F* illustrates the dominance of the flutter rhythm.

In Figure 2 at *B* carotid sinus pressure was applied. The basic dominant flutter rhythm of Figure 2*A* was abruptly interrupted and was replaced by normal sinus rhythm. The release of carotid sinus pressure at *C* shows the gradual resumption of the flutter rhythm. A chaotic pattern is shown at Figure 2*D*. At Figure 2*E* and *F* the carotid sinus pressure and release

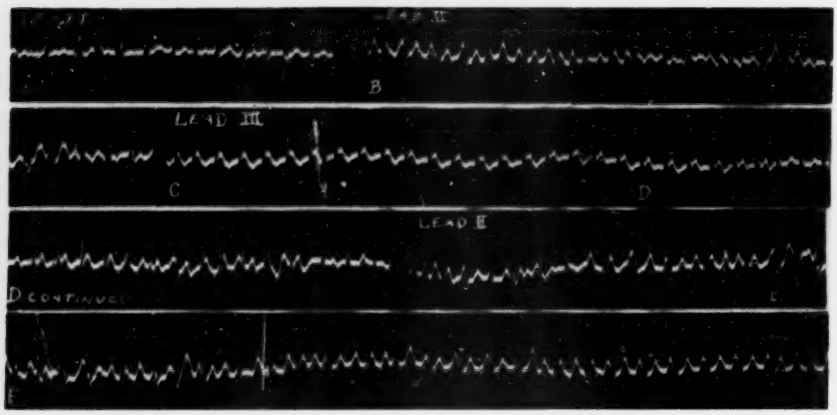


Fig. 1.—Continuous electrocardiogram of patient W. H. B. during a bout of paroxysmal arrhythmia. Auricular flutter is the dominant over-all rhythm. *A*, premature contractions arising from many foci, both auricular and ventricular; *B*, auricular flutter interspersed with ectopic foci merging into a flutter-fibrillation; *C*, flutter simulating a nodal tachycardia; *D*, point of transition to a more easily recognized auricular flutter; *E*, three successive ventricular premature contractions from different foci; *F*, dominant auricular flutter rhythm.

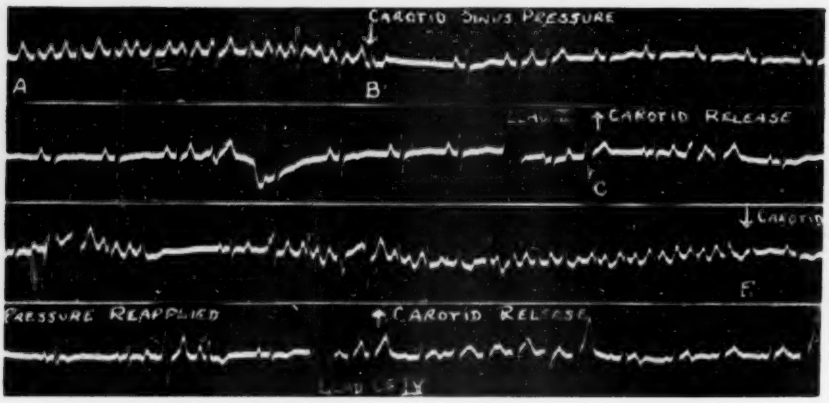


Fig. 2.—*A*, dominant auricular flutter in Lead II; *B*, carotid sinus pressure applied, with the establishment of a normal sinus rhythm; *C*, carotid sinus pressure released, with the gradual resumption of auricular flutter rhythm; *D*, chaotic heart action; *E*, carotid sinus pressure reapplied and normal sinus rhythm reestablished; *F*, carotid pressure released, with persistence of normal sinus rhythm for a short time.

was repeated with the same results, except that after release of the carotid sinus, the normal sinus rhythm continued for a longer period. (Fig. 3*A*).

Figure 3 *B*, *C*, and *D* shows the flutter rhythm with varying block. Figure 3*E* appears to show auricular fibrillation, with premature contractions again being present. At times the

differentiation between impure flutter and coarse fibrillation is a matter of opinion and is of no practical importance.

Figure 4*A* shows a paroxysm of ventricular tachycardia. Figure 4*B* demonstrates coarse fibrillation, with ventricular premature contractions at *C*. Figure 4*D* and *E* again demonstrate the carotid-sinus phenomenon already described. At Figure 4*F* the resumption of the chaotic rhythm is again seen. The minutiae of the interpretation of the arrhythmias are subject to

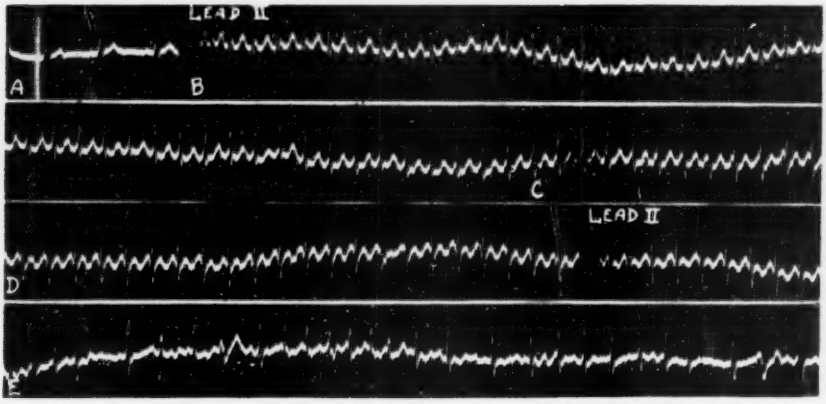


Fig. 3.—*A*, persistence of normal sinus rhythm after release of carotid pressure (Lead CF_4); *B*, dominant auricular flutter rhythm; *C*, auricular flutter with 2:1 block; *D*, continuation of auricular flutter; *E*, auricular fibrillation with occasional ventricular premature contractions.

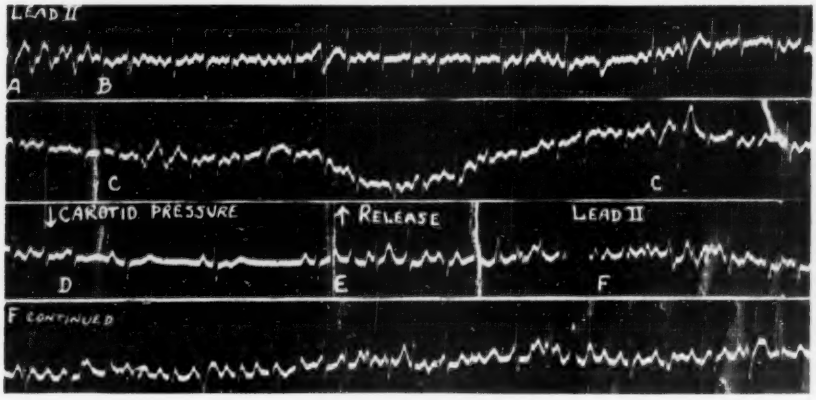


Fig. 4.—*A*, paroxysms of premature ventricular contractions resembling ventricular tachycardia; *B*, coarse auricular fibrillation; *C*, ventricular premature contractions during the auricular fibrillation; *D*, carotid sinus pressure applied and sinus rhythm established; *E*, carotid pressure released, with supervention of auricular flutter; *F*, chaotic heart rhythm.

a great deal of discussion. Several competent observers disagreed among themselves. All are agreed, however, that this arrhythmia represents a chaotic rhythm in an irritable heart. The real significance of the tracing, and the reason for this report, is the response of auricular flutter to carotid sinus pressure. A normal sinus rhythm is transiently established, and with release of the carotid sinus the arrhythmia recurs.

COMMENT

The mechanism of production of auricular fibrillation and flutter and paroxysmal tachycardia is still widely controversial. The concept that a single circus movement taking a path around the vena cava is the cause of flutter and fibrillation is far from established. Scherf [2] offers experimental evidence that the circus movement does not explain auricular fibrillation. He states that auricular fibrillation and flutter result from rapid impulse formation in a single center. Prinzmetal,[3] using a high-speed photographic technique, further demonstrated that auricular fibrillation arises from ectopic foci. Katz [1] in his discussion of the problem advances equally good reasons for supporting the theories of parasystole, of reentry, and of numerous ectopic foci, as well as the circus-movement theory, as possible explanations. Whatever the mechanism, however, there is accumulated evidence that auricular fibrillation and flutter originate and are maintained in a manner similar to that of paroxysmal tachycardia. One of the major points of difference lies in the effect of carotid sinus pressure on these arrhythmias. Ashman and Hull [4] advance the idea that paroxysmal tachycardia is due to a circus movement which passes through the auriculoventricular and sinoauricular nodes. Decherd and Herrmann [5] consider that if this should be so, then termination of paroxysmal tachycardia by reflex vagal stimulation must be the result of vagal influence on the nodal portion of the circuit. Iliescu and Sebastiani [6] reviewed the similarity of action of quinidine in cases of paroxysmal tachycardia and in those of flutter and fibrillation. The subsequent sudden change in each condition to a normal rhythm after quinidine is administered suggested to them the probability that flutter, fibrillation, and paroxysmal tachycardia might all be the result of the circus movement. Barker, Wilson, and Johnston [7] state that the sudden onset and termination of auricular tachycardia, the slowing and termination by quinidine, the stability of rate, and the occasional changes in cycle length indicate that auricular tachycardia is a circus movement. However, they point out that the cessation of the attacks by vagal (carotid sinus) pressure and digitalis suggests that it is a special type of circus movement, passing through one of the auricular nodes and differing from fibrillation and flutter.

The electrocardiographic tracing presented above, besides being of interest because of the chaotic rhythm in a patient demonstrating no apparent evidence of organic heart disease, is remarkable in that the runs of fibrillation and flutter are stopped by carotid pressure. Release of the pressure permits the reestablishment of the abnormal rhythm. This phenomenon is an exception to the accepted

2. Scherf, D.; Romano, F. J., and Terranova, R.: Experimental Studies on Auricular Flutter and Auricular Fibrillation, Am. Heart J. **36**:241, 1948.

3. Prinzmetal, M.; Corday, E.; Brill, I. C.; Sellers, A. L.; Oblath, R. W.; Flieg, W. A., and Kruger, H. E.: Mechanism of the Auricular Arrhythmias, Circulation **1**:241, 1950.

4. Ashman, R., and Hull, E.: Essentials of Electrocardiography for the Student and Practitioner of Medicine, Ed. 2, New York, The Macmillan Company, 1941.

5. Decherd, G. M., Jr., and Herrmann, G. R.: Association of Paroxysmal Atrial Tachycardia with Atrial Flutter or Fibrillation, Am. Heart J. **28**:457, 1944.

6. Iliescu, C. C., and Sebastiani, A.: The Effects of Quinidine upon Paroxysms of Tachycardia, Heart **10**:223, 1923.

7. Barker, P. S.; Wilson, F. N., and Johnston, F. D.: Mechanism of Auricular Paroxysmal Tachycardia, Am. Heart J. **26**:435, 1943.

rule that only the ventricular complexes of auricular fibrillation and flutter are slowed by carotid sinus stimulation. Hence it tends to indicate that there may be several physiological mechanisms producing paroxysmal flutter and fibrillation. From this tracing it seems that one of these mechanisms may be similar to that of paroxysmal tachycardia.

SUMMARY

An example is presented of a type of chaotic heart rhythm occurring paroxysmally in a young adult.

The electrocardiogram, which reveals an unusual pattern of arrhythmias characteristic of a chaotic rhythm, is reproduced and discussed.

Carotid sinus pressure abolished the phases of auricular flutter and fibrillation, with temporary establishment of a normal sinus rhythm.

A common mechanism or origin of paroxysmal tachycardia and of auricular flutter and fibrillation is discussed.

Termination of paroxysmal flutter and fibrillation by carotid pressure provides clinical evidence for the suggested unity of mechanisms of the arrhythmias in question or suggests the possibility that there may be several physiological mechanisms producing similar patterns.

PULMONARY GRANULOMATOSIS FOLLOWING EXTENSIVE USE OF PARADICHLOROBENZENE

RUSSELL W. WELLER, M.D.
AND
ANTRIM J. CRELLIN, M.D.
PHILADELPHIA

TO THE best of our knowledge the case herein reported is the first instance of pulmonary granulomatosis occurring in man or experimental animals exposed to the vapors of paradichlorobenzene.[1] The wide use of this and related chemical compounds in the home and in industry as insecticides, particularly as moth preventives, renders any suspected toxic properties worthy of investigating and reporting.

Teramoto [1] exposed guinea pigs for several months to paradichlorobenzene vapors, with slight, apparently insignificant, histological changes.

Berliner [2] believed that cataracts, hepatitis, and loss of weight followed exposure to this chemical in two patients he observed. It may be noted that neither patients died and studies of the organs with the exception of the eye lens were not available. Berliner also exposed rabbits and guinea pigs to paradichlorobenzene for periods of one to four months. Pneumonia was found in one guinea pig, and midzonal liver damage was found in all guinea pigs. The rabbits also showed central necrosis of the liver and no changes in lungs, adrenals, kidneys, or bone marrow. No lens opacities developed in the animals breathing the fumes of the drug.

Ballotta and Mattioli [3] exposed rabbits to vapors of the compound periods up to two months and after pathological studies of the various organs concluded that the vapors were harmless.

Perrin [4] reported a case of intoxication in a human being due to the wearing of clothes impregnated with paradichlorobenzene. The clinical picture included vertigo, asthenia, anemia, and granulocytopenia.

Pike [5] exposed rabbits to the compound for 62 eight-hour periods and studied eye changes carefully. Although toxic eyeground changes were produced, no lens changes were observed.

From the Departments of Pathology and Medicine, Hahnemann Medical College and Hospital.

1. Teramoto, M.: Nagoya J. M. Sc. **7**:69, 1933; Biol. Abstr. **10**:13482, 1936.
2. Berliner, M. L.: Arch. Ophth. **22**:1023, 1939.
3. Ballotta, F., and Mattioli, P.: Arch. ital. Sc. farmacol. **10**:65, 1941; abstracted, Chem. Abstr. **37**:2815, 1943.
4. Perrin, M.: Bull. Acad. méd. Paris **125**:302, 1941; abstracted, Chem. Abstr. **37**:3833, 1943.
5. Pike, M. H.: J. Michigan M. Soc. **43**:581, 1944.

Zupko and Edwards[6] exposed rabbits, rats, and guinea pigs to paradichlorobenzene vapors for periods up to 31 days and produced intoxication characterized by eye and naris irritation, tremors, and death in many of the animals. Hematological study indicated that the compound caused granulocytopenia in a majority of the animals, although erythrocytes were not greatly affected. The blood picture became normal within 30 days after exposure. Tissue studies, particularly of the lungs, are described briefly, and little if any interpretation is possible from the photomicrographs submitted. The authors felt, however, that definite glomerular and tabular damage was present in the kidneys. The lungs were said to be congested, edematous, and hemorrhagic in the guinea pigs, and in addition in the rabbits a "true pneumonia" was said to be present.

REPORT OF A CASE

A 53-year-old white woman was first hospitalized at another institution in October, 1948, with a cough and progressive dyspnea, which had begun about one year before. She was afebrile and recovered slowly, but her cough remained and was productive of mucoid sputum. Her second hospitalization was in October, 1949, at which time she complained of the same symptoms. She was treated with aureomycin to no avail. While she was in the hospital, although no bronchoscopy was done, a diagnosis of moniliasis was made. She received large doses of potassium iodide, which gave her no relief but did increase the amount of mucoid sputum. Her third hospitalization was in January, 1951; she had the same symptoms and was again treated for moniliasis. She remained in the hospital for three weeks. No improvement was noted, and she returned home.

She was first admitted to Hahnemann Hospital March 2, 1950, complaining of dyspnea, fatigue, and cough, which were especially severe in the mornings and were paroxysmal the remainder of the day. The sputum was mucoid, odorless, and tasteless. She raised 2 to 3 oz. of sputum in 24 hours. Wheezing had been present intermittently since 1948. Her history and family history were irrelevant. There was no significant occupational history.

The temperature, pulse, respirations, and blood pressure were normal. Physical examination revealed a normal heart with the exception of an accentuation of P_2. There was no cardiac enlargement. The abdomen was normal. No enlarged lymph nodes were palpable. The nose, throat, and extremities were normal. Pelvic and rectal examinations were negative. Examination of the lungs showed moderate hyperresonance and diminished breath sounds throughout both lung fields. Over the lower two-thirds of both lung fields anteriorly and posteriorly there were fine rales associated with minimal wheezing.

Bronchoscopic examination revealed no abnormal findings, and it was necessary to lavage the bronchial tree in order to obtain an adequate specimen for bacteriologic examination.

The results of laboratory examinations were as follows: The blood urea, sugar, total serum protein, and albumin-globulin ratio were normal. The Kolmer and Kahn tests were negative. The urine and the blood sedimentation rate were normal. The vital capacity was 1,100 cc. The reaction to P. P. D. No. 1 was negative and that to P. P. D. No. 2 was positive. The hemoglobin content was 14.0 gm. The erythrocytes numbered 5,000,000 per cubic millimeter and the leucocytes 6,600, with polymorphonuclear neutrophiles 66%, lymphocytes 32%, monocytes 1%, and polymorphonuclear eosinophiles 1%. Smears of aspirated bronchial secretions did not show malignant cells, fungi, or tubercle bacilli. Several sputum specimens were examined for tubercle bacilli, and the results were negative. Cultures of the sputum as well as of the aspirated bronchial secretions for common bacteria, tubercle bacilli, and fungi were negative. A complete gastrointestinal series, including use of a barium sulfate enema, showed nothing abnormal. A posterior-anterior upright film of the chest showed a diffuse ground-glass haziness throughout both lung fields. In the right upper mediastinum, there was a shadow which was interpreted as an enlarged

6. Zupko, A. G., and Edwards, L. D.: A Toxicological Study of p-Dichlorobenzene, J. Am. Pharm. A. (Scient. Ed.) **38**:124, 1949.

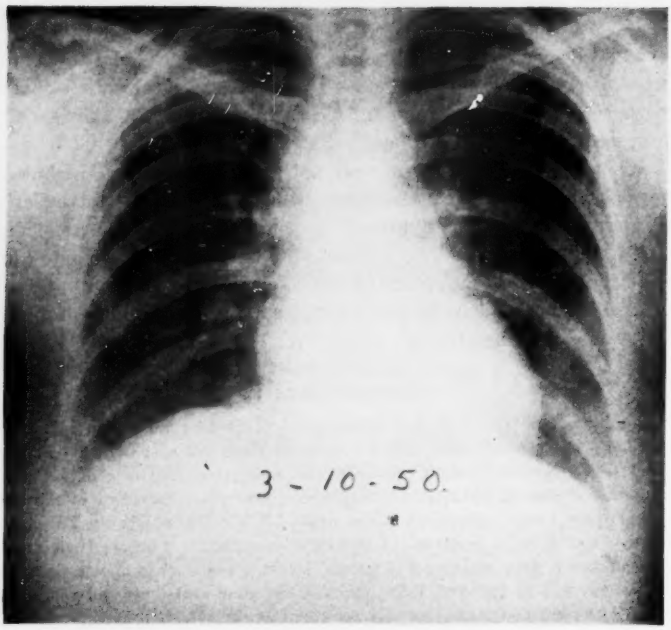


Fig. 1.—Posterior-anterior view, showing diffuse ground-glass haziness throughout both lung fields and a shadow in the right upper mediastinum.

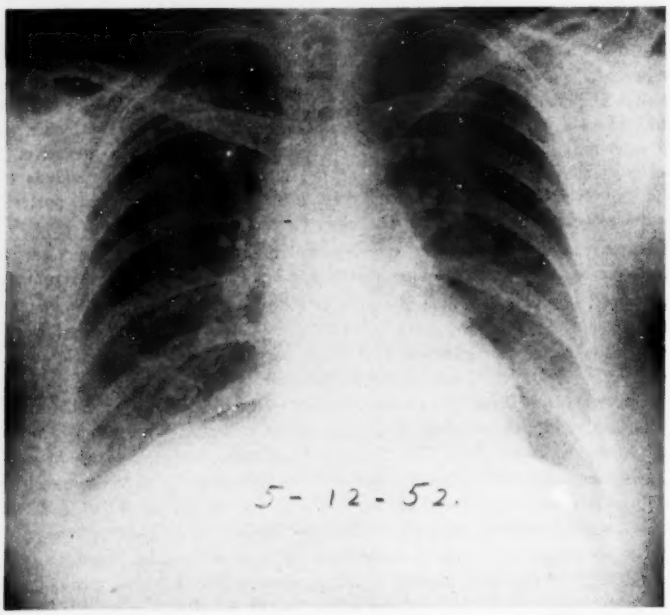


Fig. 2.—Posterior-anterior view of lungs, showing slight increase in diffuse ground-glass haziness.

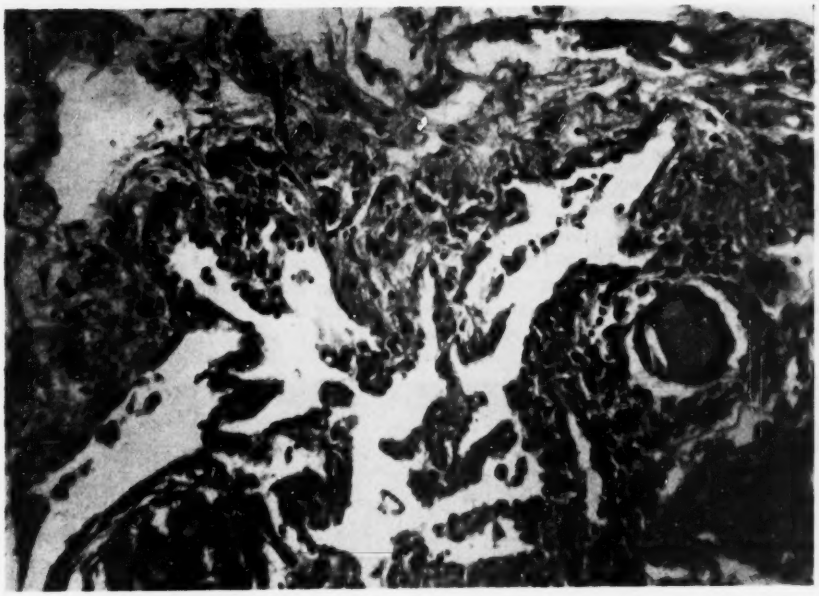


Fig. 3.—Lung specimen showing granulomatous reaction, with a foreign-body giant cell containing a crystal. × 100.

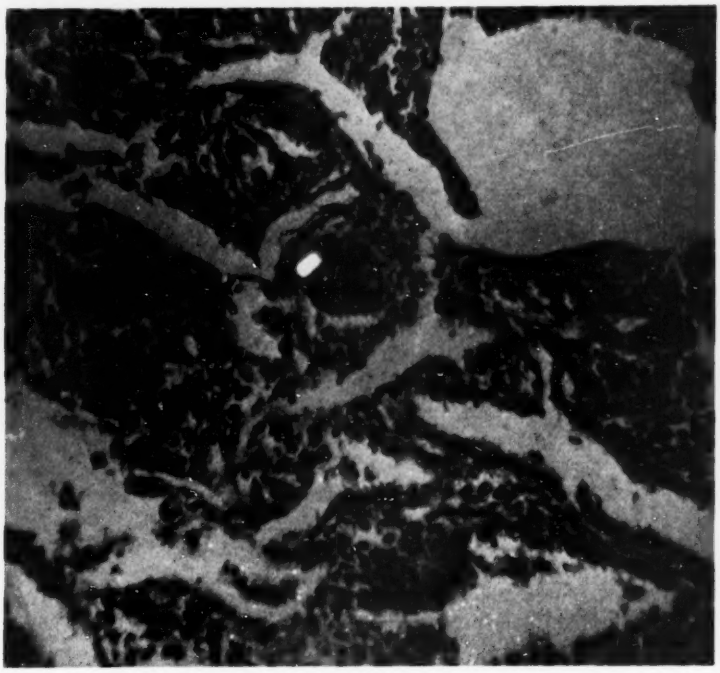


Fig. 4.—Another area of lung, showing birefringence of crystal in polarized light. × 100.

gland, probably paratracheal (Fig. 1). Fluoroscopically, the hemidiaphragms moved poorly. The electrocardiogram was normal. X-ray study of both hands and feet gave negative results.

The patient was advised at this time to have an exploratory thoracotomy and a lung biopsy in order to substantiate or disprove a provisional diagnosis of Boeck's sarcoid. This procedure was refused.

The patient was seen on several occasions after her hospitalization, but eventually failed to keep her appointments. On May 12, 1952, she returned for examination and requested a lung biopsy. There was little change in her condition, with the exception of slight cyanosis and increased dyspnea. The vital capacity was 1,000 cc. Physical examination disclosed no change. A posterior-anterior upright film of her lungs showed a slight increase in the diffuse haziness in both lung fields (Fig. 2). She had had one admission to another hospital in the interim; at that hospital she was not seen by any of us and was again treated for moniliasis.

Fig. 5.—Specimen of rabbit lung showing acute hemorrhagic pneumonitis and crystals. × 100.

She was admitted to Hahnemann Hospital on June 30, at which time Dr. R. P. Glover, through a 10-cm. submammary incision, did an exploration of the left lung together with amputation of a generous portion of the tip of the lingula. No growths were encountered in the parenchyma of the lung. The pleural surfaces were smooth and thin. The hilus was free and mobile. The lung felt thickened and fibrotic and was of a rubbery texture, but no gross lesions or nodules could be palpated. Her recovery was uneventful, and she was discharged July 9.

The specimen was studied in the bacteriology and pathology laboratories. Smears and cultures of material from the lung revealed no fungi, common bacteria, or tubercle bacilli.

The specimen consisted of a wedge-shaped piece of lung measuring 4.5 by 2 by 1.5 cm. The pleural surface was smooth and glistening and was not thickened. The cut surface was mottled reddish-gray and rubbery.

Microscopic examination of lung tissue revealed diffuse distortion of the architecture due to the presence of numerous small lesions which had a distinctive microscopic appearance. Their centers were made up of prominent plate-like crystals. These crystals were often surrounded by granular blue-staining material probably representing calcium. Around these masses there were fibrous-tissue proliferation and foreign-body giant cells. Some of the giant cells contained similar crystals within their cytoplasm (Fig. 3).

Examination with polarized light revealed that the crystals were birefringent plates similar to crystals of paradichlorobenzene (Fig. 4). The surrounding lung parenchyma showed distortion due to fibrosis, with thickening of alveolar walls and infiltration by large numbers of lymphocytes and mononuclear phagocytes. The bronchi were not remarkable, but there were slight to moderate thickening of the muscular walls of the small arteries and focal fibrous thickening of the pleura.

The microscopic findings made us suspicious that the patient might be inhaling some foreign material in her home. Upon carefully quizzing the patient we found that for 12 to 15 years she had been using paradichlorobenzene in large amounts. The exact quantity was unknown. She scattered the crystals upon all upholstered furniture and carpets once a week. In addition she used them in closets about four times a year. For the past three years the crystals were vaporized in a modern vacuum cleaner once a week. The husband stated that the house constantly smelled of the moth eradicator.

After the operation there was no change in her symptoms or in the roentgenological findings.

Chemical analysis of the tissue for paradichlorobenzene was rendered inaccurate because of formaldehyde fixation.

This case, even though not specifically proved, seems to merit a presumptive diagnosis of pulmonary granulomatosis due to inhalation of paradichlorobenzene vapor when the history and physical properties of the crystals in the lung are objectively evaluated.

Experimental studies are now under way in our laboratory in which New Zealand white rabbits are being exposed to paradichlorobenzene vapors for periods up to the life span of the animal. The vapors are produced from crystals placed beneath the mesh floor of the pens. One rabbit died after one week of exposure, and autopsy revealed no significant gross changes except diffuse hemorrhagic pneumonia of both lungs. The eyes were not remarkable. Owing to formalin fixation, chemical examination of the lungs or other viscera was not possible.

Microscopic examination of the lungs revealed moderate edema, many erythrocytes, and moderate numbers of polymorphonuclear leucocytes, lymphocytes, and monocytes within alveolar walls and adjacent portions of alveoli. Crystals were present within this exudate similar to those seen in the patient's lungs (Fig. 5). Sections from the liver, although somewhat distorted because of autolytic change, revealed focal necrosis, which in some lobules was central and in others was midzonal. Sections from the remaining viscera were not remarkable.

SUMMARY

A case of pulmonary granulomatosis in a woman with a history of prolonged, heavy exposure to paradichlorobenzene moth crystals is presented. Microscopically, crystals were present in the patient's lung lesions which were physically similar to those of paradichlorobenzene.

A rabbit that died after short exposure to paradichlorobenzene vapors had acute pneumonia, with similar crystals in the pneumonic exudate.

Further investigation of the possible toxic effects of this chemical appears to be warranted.

Correspondence

BACITRACIN

To the Editor:—The review of the booklet on bacitracin which appears on page 424 of the September issue of the ARCHIVES OF INTERNAL MEDICINE has recently been brought to my attention. I should like to point out some fallacies in that review.

The reviewer says that there are "many statements in this book which are hardly warranted on the basis of present-day knowledge," but he has not pointed out one such statement. Those that he uses as illustrations are inaccurate. Contrary to what the reviewer has stated, the book covers fully all of the studies on the nephrotoxic element in bacitracin reported up to the time of publication. Furthermore, nowhere in the book is the statement made that bacitracin is the treatment of choice in amebiasis.

Contrary to what the reviewer has stated, (1) nephrotoxicity was of minor importance in the last 250 cases reported; (2) the purity of the manufactured product has steadily increased while the toxicity has steadily decreased; (3) the Food and Drug Administration has consented to its systemic use in hospitals for more than a year, and (4) bacitracin is only slightly absorbed from the alimentary tract and materially cuts down the coccal and clostridial flora of the intestine.

The book makes no pretenses. It is an accurate and complete review of all of the published literature on bacitracin up to the date of its publication. Such statements as those the reviewer has made cast aspersions on the honesty and integrity of the authors of the articles quoted and of the medical journals in which the reports have appeared. These include men of the highest qualifications and journals of the highest rank.

FRANK L. MELENEY, M.D., New York (32).

To the Editor:—I wish to comment on the review of a book on bacitracin, published on page 424 in the September, 1952, issue of the ARCHIVES OF INTERNAL MEDICINE.

I have no personal interest in the publishers of the book, nor in bacitracin, with the exception that I did a good deal of work with this antibiotic. I do not believe that the reviewer's implication that bacitracin is made to be the drug of choice in the treatment of amebiasis by the book is justified on the basis of what is said in the book.

I believe that if the reviewer refers to the papers published on the therapy of amebiasis with bacitracin, he will find it stated that cure rates following use of this drug are approximately 65% and that the drug is apparently quite active in some instances in terminating episodes of acute ulcerative amebic colitis. Obviously, this drug is not the drug of choice in the treatment of amebiasis.

HARRY MOST, M.D., New York (16).

News and Comment

ANNOUNCEMENTS

New Civil Service Examination.—The United States Civil Service Commission has announced a new examination for medical officers for filling positions in various specialized fields of medicine, with salaries ranging from $5,940 to $10,800 a year. The positions are principally in the Bureau of Indian Affairs located on reservations west of the Mississippi River and in Alaska. A few positions may be filled in the Fish and Wildlife Service. Applicants must be fully qualified as doctors of medicine, and, for most positions, must be currently licensed to practice medicine and surgery in a State or Territory of the United States. Appropriate experience is required.

Further information and application forms may be obtained from the U. S. Civil Service Commission, Washington 25, D. C., or from most first- and second-class post offices. Applicants will be accepted until further notice by the Board of U. S. Civil Service Examiners, Bureau of Indian Affairs, Department of the Interior, Washington 25, D. C.

American Board of Nutrition, Inc.—The American Board of Nutrition, Inc., will meet in April, 1953, to consider applications of candidates for certification as specialists in human nutrition. Completed applications should be in the office of the Secretary not later than March 15. Candidates who are deemed eligible for examination will be notified of the date, place, and procedure of the examination, after the meeting of the Board. Application forms may be obtained from the Secretary, Otto A. Bessey, School of Medicine, The University of Texas, Galveston, Texas.

The complete list of specialists in human nutrition, certified by the Board as of current date, may be found in the February, 1953, issue of the *Journal of Clinical Nutrition*.

GENERAL NEWS

Dr. Joseph Hersey Pratt Celebrates Eightieth Birthday.—Dr. Joseph Hersey Pratt, clinician, investigator, teacher, author, and humanitarian, celebrated his eightieth birthday on Dec. 5, 1952.

He is the author of approximately 150 medical publications. The most important of these have dealt with the bacteriology and diagnosis of typhoid, the bed-rest treatment of tuberculosis, the external function of the pancreas, gout, hydrotherapy, the action of digitalis, and group psychotherapy.

Dr. Pratt was a pioneer in employing prolonged bed rest in the treatment of pulmonary tuberculosis, and many years passed before it gained general recognition. In 1905 Dr. Pratt organized in his clinic at the Massachusetts General Hospital a "tuberculous class" for the treatment of poor tuberculous patients. The latter carried out Dr. Pratt's treatment of prolonged absolute rest in their homes, where they were instructed by a paid full-time nurse, called by Dr. Pratt a "friendly visitor." Dr. Pratt met these patients once a week in a group at the hospital. This "class method" of treating patients was revolutionary in character and introduced the use of group as well as medical social work in the practice of medicine. Dr. Pratt is, therefore, considered the pioneer of group therapy, a method which attracted the attention of the medical profession here and abroad.

He played an important part in the introduction of bedside training of Harvard medical students at the Massachusetts General Hospital.

Dr. Pratt reported the first case in the United States of infection with the paratyphoid B bacillus. He contributed to the reintroduction of pneumothorax as a therapeutic agent in this country.

In 1931, with the financial aid of Mr. William Bingham II, Dr. Pratt founded a diagnostic hospital in connection with the Boston Dispensary.

His many friends, disciples, and admirers wish him many more years of happiness, health, and creative activity.

Books

Toxoplasmosis: Pathology of Neonatal Diseases; Pathogenesis, Diagnosis, and Treatment. By Jacob Karl Frenkel, M.D., Ph.D., and Saul Friedlander, M.D. Price, $0.50. Pp. 107, with 91 illustrations. Public Health Service, U. S. Government Printing Office, Washington 25, D. C., 1951.

This excellent monograph describes in detail the clinical histories of five fatal and two nonfatal cases of neonatal toxoplasmosis, with autopsy findings of four of the fatal cases. Serological and immunological data from six patients and their families are compared and the course of dye and complement-fixing antibody titers charted. The pathology and pathogenesis of typical lesions are described accurately and in considerable detail. Methods of diagnosis and their interpretation are described. The bibliography contains 184 references, and there are 36 plates of photomicrographs. For anyone interested in toxoplasmosis this is an accurate text with an abundance of detailed information.

Diseases of Metabolism. Edited by Garfield G. Duncan, M.D., with many contributors. Third edition. Price, $15.00. Pp. 1179, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1952.

That a third edition of Duncan's "Diseases of Metabolism" should be called for shows the well-deserved popularity which has been won by this book. The critical chapters on carbohydrate, protein, lipid, and mineral metabolism by Soskin, White, and Cantarow make a splendid introduction. Peters has an authoritative section on water balance, as do Spies and Butt on vitamins and avitaminosis. The more clinical chapters, by Duncan and others, are authoritative and well written; the reviewer is not quite clear why diseases of the thyroid rather than of the adrenal or pituitary are included, or indeed diseases of the kidney. Well, the buyer gets just that much more for his money. The book is well printed and illustrated and is generally attractive.

Renal Function: Transactions of the Third Conference October 18-19, 1951. Edited by Stanley E. Bradley, M.D. Price, $3.50. Pp. 210, with illustrations. Josiah Macy, Jr Foundation.

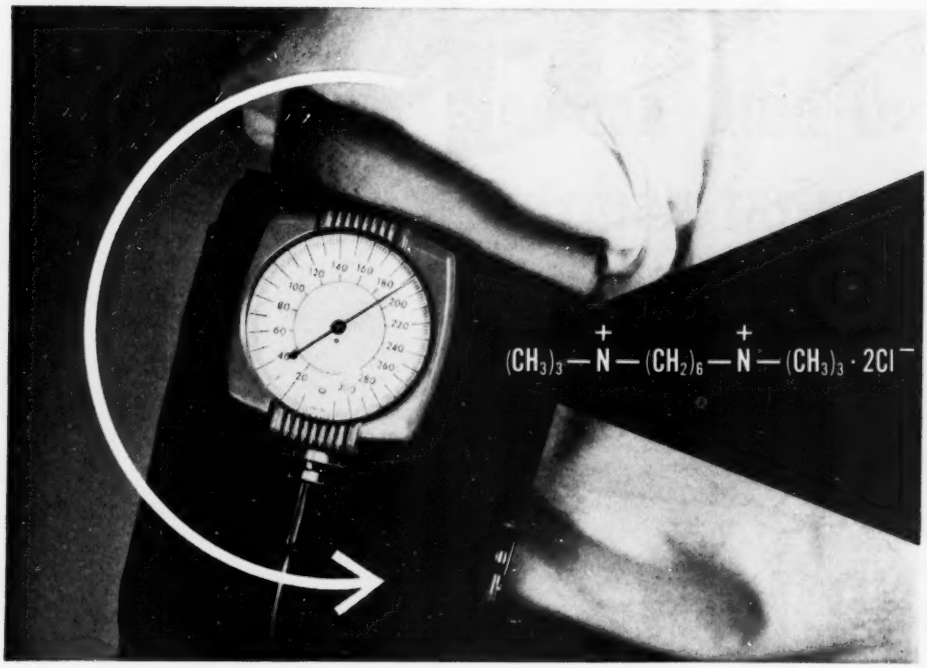
The contents includes discussions by J. R. Pappenheimer on the passage of substances across capillary walls; by F. P. Chinard on the mechanisms of formation of glomerular fluid, by F. R. Winton on intrarenal pressure and renal blood flow; by E. E. Selkurt on physical factors in relation to electrolyte and water excretion; by J. P. Merrill on the use of the artificial kidney; by R. W. Berliner on tubular secretion of potassium and acid, and by J. V. Taggart on enzymatic processes in tubular secretory transport.

There is a large amount of specialized data along with interesting discussion. This material is intended for investigators in the field of renal function and will serve this purpose well.

Veterans Administration Technical Bulletins Series 10. Various authors. Price, not given. United States Government Printing Office, Washington 25, D. C., date not given.

This Bulletin contains brief but well-written articles on a variety of medical topics by well-known authorities.

Outstanding are the discussion of "Sarcoidosis" by Longcope, the "Diseases of Collagen" by Baehr and Levitt, "Barbiturate Intoxication" by Isbell, the "Differential Diagnosis of Vertigo" by Lindsay, and "Diagnosis and Management of Pyogenic Meningitis" by Daniels and MacMurray.



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1. Grimson, K. S., et al.: J.A.M.A. *149*:215 (May 17) 1952.

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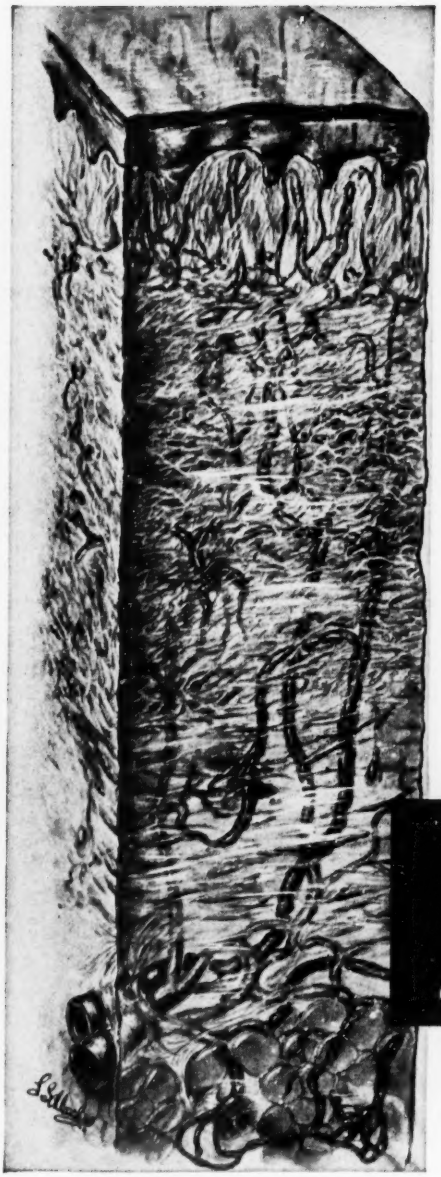

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1. Bargen: Chronic Ulcerative Colitis. Charles C Thomas, Publisher. 1951. Springfield, Illinois.

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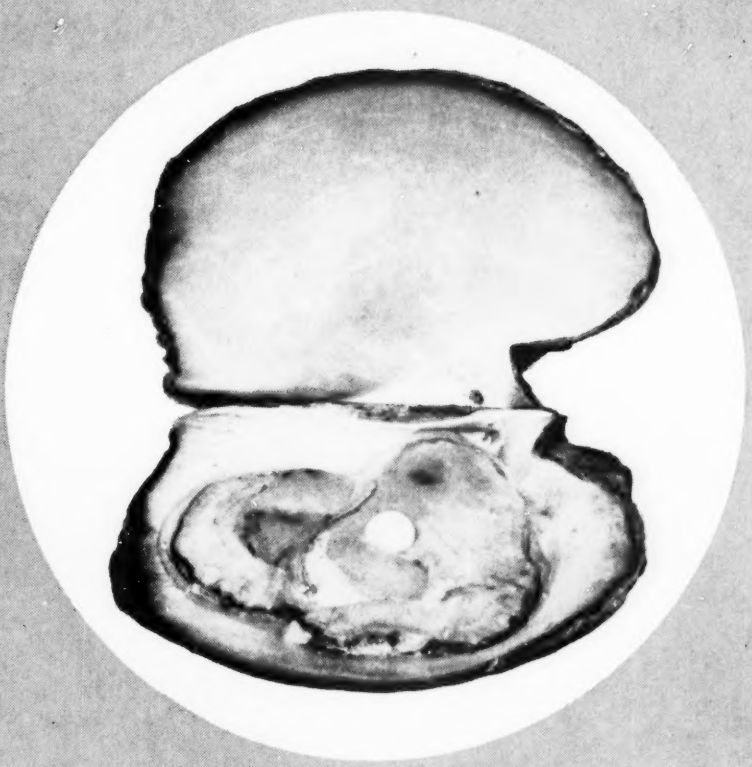

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(phentolamine methanesulfonate Ciba), preferred in the diagnosis of pheochromocytoma, the cause of the most common form of hypertension of *known* etiology. The injection of this *adrenergic blocking agent* affords an accurate test that is relatively safe, and can be simply performed by any physician, unassisted, in his office.

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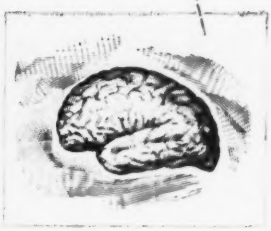
Complete information can be obtained by writing to the Medical Service Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.



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hydrochloride (hydralazine hydrochloride Ciba), an agent of choice (for use) in the treatment of hypertension. This orally effective antihypertensive is believed to act *centrally* to produce a gradual, sustained decrease in blood pressure while increasing blood flow through the kidneys.

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